UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

HELSINN HEALTHCARE, S.A. and ROCHE PALO ALTO, LLC,

Plaintiffs,

-vs-

DR. REDDY'S LABORATORIES, LTD., DR. REDDY'S LABORATORIES, INC., TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES, LTD.

Defendants.

CIVIL ACTION NUMBER:

11-3962

TRIAL

Clarkson S. Fisher United States Courthouse
402 East State Street
Trenton, New Jersey 08608
June 5, 2015

B E F O R E: THE HONORABLE MARY L. COOPER
UNITED STATES DISTRICT JUDGE

Certified as True and Correct as required by Title 28, U.S.C., Section 753

/S/ Regina A. Berenato-Tell, CCR, CRR, RMR, RPR
/S/ Carol Farrell, CCR, CRR, RMR, CCP, RPR, RSA

A P P E A R A N C E S:

PAUL HASTINGS
BY: JOSEPH O'MALLEY, ESQUIRE
ERIC W. DITTMANN, ESQUIRE
SAUL EWING
BY: CHARLES M. LIZZA, ESQUIRE
Attorneys for the Plaintiffs

BUDD LARNER
BY: STUART D. SENDER, ESQUIRE
MICHAEL H. IMBACUAN, ESQUIRE
HUA HOWARD WANG, ESQUIRE
CONSTANCE S. HUTTNER, ESQUIRE
KENNETH E. CROWELL, ESQUIRE
Attorneys for the Defendant, Dr. Reddy's Laboratories

WINSTON & STRAWN
BY: JOVIAL WONG, ESQUIRE
GEORGE LOMBARDI, ESQUIRE
JULIA MANO JOHNSON, ESQUIRE
BRENDAN F. BARKER, ESQUIRE
LITE DePALMA, GREENBERG, LLC
BY: MAYRA V. TARANTINO, ESQUIRE
Attorneys for the Defendant, Teva

I N D E X

(In open court. June 5, 2015, 9:30 a.m.)

THE COURT: Good morning, everyone.

ALL: Good morning, your Honor.

THE COURT: Shall we continue?

MR. WONG: Yes.

THE COURT: Call your witness, Mr. Wong.

MR. WONG: Good morning, your Honor.

THE COURT: Call your witness, Mr. Wong.

MR. WONG: Sorry. I didn't hear you.

Just a bit of housekeeping. There were some exhibits that we didn't move into evidence yesterday from Dr. Fruehauf's testimony. If we can move them into evidence now. Just a couple of Exhibits. They are DTX-0015, DTX-0289 and DTX-0290.

MR. O'MALLEY: No objection.

THE COURT: Thank you. Those are admitted into evidence.

Just so you know, I have conferred with the court reporters and have told them not to put into the transcripts the admission of individual exhibits. Instead, we will rely upon the signed list that the parties give us at the end of the trial.

MR. WONG: Understood. Thank you.

Your Honor, today we're going to shift gears a little bit and talk about the obviousness of the claim formulations.

As our first witness, defendants call Dr. Lee Kirsch.

(Whereupon, LEE EDWIN KIRSCH, witness for the Defendant Teva, sworn.)

THE DEPUTY CLERK: Please state and spell your full name for the record. Have a seat.

THE WITNESS: My name is Lee Edwin Kirsch, K-I-R-S-C-H.

LEE EDWIN KIRSCH, DEFENDANT TEVA'S WITNESS, SWORN,

VOIR DIRE EXAMINATION BY MR. WONG:

Q. Good morning, Dr. Kirsch.

A. Good morning.

Q. Dr. Kirsch, have you been asked to provide expert opinions in this case?

A. I have.

Q. And, in general, what do your expert opinions relate to?

A. They relate to the formulation in question and the invalidity of that formulation based on obviousness.

Q. Thank you. Let's review some background.

Dr. Kirsch, where are you currently employed?

A. I'm at the University of Iowa, faculty member at the University of Iowa in the College of Pharmacy.

Q. And what is your current position at the College of Pharmacy?

A. I'm a professor in the division of pharmaceutics and translational therapeutics.

Q. And how long have you been at the University of Iowa College of Pharmacy?
A. A little over 20 years.
Q. Dr. Kirsch, where did you attend college?
A. I did my undergraduate work at Purdue University and did my graduate work at Ohio State University.
Q. Okay. And at Purdue, what degree did you receive?
A. I received a B.S. in science in pharmacy and pharmacal sciences.
Q. And at the Ohio State University, what was your degree?
A. I received a Ph.D. in pharmaceutical chemistry.
Q. And what year --
THE COURT: How long has this general field been available in academics? You know, like when you majored in science, pharmacy and pharmaceutical sciences?
THE WITNESS: I think it's been around since relatively early in the last century. You know, the various disciplines in pharmacy, you know, typically include pharmacology and medicinal chemistry. And pharmaceutics, which is sometimes at Ohio State it was called pharmaceutical chemistry, which has to do with more of the physical chemistry of pharmaceutical systems. And then there's clinical pharmacy, as well.
THE COURT: What is pharmacology as distinguished from clinical pharmacy?

THE WITNESS: So, pharmacology deals with the pharmacological or the activity of a drug substance in the body, and clinical pharmacy deals with, you know, the therapeutic use of those drug substances in a clinical setting.

THE COURT: Interesting. I hear those words, but we don't really know what the shades of meaning are.

Thank you.

BY MR. WONG:

Q. When did you receive your Ph.D.?

A. 1982.

Q. And what was the thesis of your Ph.D.?

A. My thesis involved the degradation kinetics and mechanisms of a -- and pharmacokinetics of a cancer prodrug.

Q. After you got your Ph.D., what did you do?

A. I joined the parenteral products development group in the pharmaceutical development division of Eli Lilly and Company.

Q. And how long were you -- did you work at Eli Lilly?

A. I was at Eli Lilly for 12 years as an industrial scientist.

THE COURT: In Indianapolis?

THE WITNESS: In Indianapolis, correct.

BY MR. WONG:

Q. You mentioned the parenteral product division. What is a parenteral product?

A. Parenteral products are typically injectable products, as distinguished from orally administered products.

Q. And what do injectable products include?

A. What do they include? So, you know, they would include I.V. formulations; IM, intramuscular, formulations; subcutaneous formulations. We also did some work in topical formulations.

Q. And during your time at Eli Lilly, what was your role in pharmaceutical development?

During your time at Eli Lilly, what was your role in pharmaceutical development?

A. Well, I was a formulation scientist. My role was to develop formulations that would be used in clinical trials and, ultimately, in -- for commercial use.

Q. What were some of the activities that you practiced during your time at Lilly in pharmaceutical development?

A. Well, the pharmaceutical scientist is involved in various phases of the pharmaceutical development process, so we would do chemical characterization of the active drug substance.

We would also develop formulations that were going to be used in the clinical studies and, ultimately, in commercial use.

And we would also assist in the clinical supply of drug products for clinical studies.

Q. By the end of your career at Eli Lilly, what was your

title?

A. I was a group leader, so I had six or so scientists and technologists that reported to me, and my title was senior research scientist.

THE COURT: Your scientists that reported to you at that time, would they have had advanced degrees or equivalent experience?

THE WITNESS: Yes. So it was, you know, frequently the case that new Ph.D.s would serve some time in someone else's group.

So I would have Ph.D. scientists that reported to me, as well as masters and bachelor-level scientists. And then we also had a few technicians who either had associate degrees or, you know, just had a fair amount of experience in the laboratory.

THE COURT: These were lab tech --

THE WITNESS: Yeah, lab tech individuals.

THE COURT: Okay. Any animal labs under you at that time?

THE WITNESS: We worked with animal labs. We collaborated with animal labs, but we didn't do animal studies in our laboratory.

BY MR. WONG:

Q. Okay. During your 12 years at Eli Lilly, did you participate in any project teams?

A. Yes. You know, I participated in about 20 or so project teams during my time at Lilly.

Q. And what is a project team?

A. So, a project team is a group of scientists and experts or people practice in the people that come together to deal with all of the requirements of developing a pharmaceutical product.

So this group would likely include, or would include, you know, clinical scientists. It would include toxicologists, process chemists, analytical chemists and formulation chemists and scientists, as well. And there would also be marketing individuals that would participate in the project team.

Q. And, so, to be clear, who on the project team would be responsible for developing the actual formulation of the drug?

A. That would be the responsibility of the formulation scientist.

Q. And when you participated in a project team, would that be yourself?

A. Yes, that's correct.

Q. During your time at Eli Lilly, what kind of drug products or drug molecules did you work with?

A. A lot of the work that I did was in the peptide and peptide hormone field. At that time, you know, recombinant technologies were becoming -- they were becoming

commercialized, so a lot of the compounds that I dealt with were peptides, antibiotics, and hormones.

We also dealt with -- I also dealt with small molecules, as well, small organic molecules.

Q. And, so, for these compounds, what was the focus of your work from a formulations perspective?

A. So, the focus of my work was to -- was to evaluate these compounds and then design and optimize formulations that could be used, again, in the clinic and then subsequently for commercial use.

So we would supply the necessary information and background for the Investigational New Drug Applications and also for the NDAs.

Q. Okay. You mention about 20 project teams you worked on during your time at Lilly.

About how many of those projects made it to final FDA approval?

A. Well, there were probably six or so.

Q. And out of the remaining products that didn't make it to FDA approval --

THE COURT: Projects?

BY MR. WONG:

Q. -- projects, were any of those due to formulation issues?

A. No. We were always able to come up with suitable formulations for those compounds. Typically, the reason why

compounds would fail was because of an efficacy or a safety issue at some point.

Q. So, after your 12 years at Lilly, what did you do?

A. So, after my time at Lilly, I joined the faculty at the University of Iowa, and I have been there ever since.

Q. Okay. At Iowa, are you responsible for teaching?

A. Yes. I participate in teaching both at the pharmacy, professional pharmacy degree level and also in the -- in the graduate school.

Q. Do you also perform your own research at Iowa?

A. That's correct. A large section of my time is devoted to my research laboratory.

I have a group of graduate students and post-docs who participate in research activities under my direction in my laboratory.

THE COURT: The pharmacist at the local drugstore --

THE WITNESS: Yes.

THE COURT: I'm not talking about the helpers back there. I don't know what their credentials are, but I would think that there would have to be a pharmacist in charge of every, you know --

THE WITNESS: That's correct.

THE COURT: -- drugstore lab.

Do they get their education at a school of pharmacy such as yours?

THE WITNESS: Yes. That's correct. The degree that they get now is a Pharm.D. it's a Doctor of Pharmacy.

THE COURT: Really?

THE WITNESS: Yes. It is a four-year program. So, typically --

THE COURT: It's a four-year undergraduate program?

THE WITNESS: No. Typically, they would come in with two to four years of undergraduate training before they enter the College of Pharmacy, and then the pharmacy program leads them to what's called a Doctor of Pharmacy, right. So it's, you know, a six- to eight-year program typically.

THE COURT: Yours is a Ph.D.?

THE WITNESS: Mine's a Ph.D., right.

Right. And at the time, I did my -- I also was a pharmacist for a few years between my undergraduate and graduate education. At that time, the degree requirement was a bachelor of science in pharmacy to become a pharmacist, so it was actually a five-year program rather than a four-year program, but it's now gone to a Pharm.D.

THE COURT: And that's for every CVS that we drive by?

THE WITNESS: Yes. That's correct.

THE COURT: Okay.

BY MR. WONG:

Q. For your research, what is the primary focus of your

research?
A. Well, a good portion of my research is focused on studying the kinetics and mechanisms of drug degradation processes, and that's a major focus for my research.
Q. And as part of your research, do you collaborate with industry still?
A. Yes.
So, my research is funded with a combination of government funding. Recently, I've had funding from National Science Foundation and a fair amount of funding from the FDA, but another portion of my funding comes from industrial contracts, so we do -- we work on problems that the industry brings to us.
Q. Okay. And for teaching your students, you mentioned your pharmacy students and Ph.D. graduate students?
A. That's correct.
Q. So, for your pharmacy students, what is the degree that they're getting?
A. They're getting a Doctor of Pharmacy degree, professional degree.
Q. And what are the options for their professional practice afterwards?
A. So, the majority of them will go into community practice, for instance, at a CVS type of situation.
Another substantial fraction of them will go into

clinical practice in a clinical setting in a hospital setting.

And then a few of them will end up in the industry or in a regulatory agency.

Q. Okay. And what kind of courses or subject matters do you teach those professional students?

A. So, the focus of my teaching there is really in two areas. I teach them about pharmaceutical products, you know, what's the composition and performance characteristics of pharmaceutical products, and I also teach pharmacokinetics to pharmacy students. I typically also teach a section on drug stability.

Q. Okay.

THE COURT: Pharmacokinetics?

THE WITNESS: Yeah. So pharmacokinetics describes the -- what happens to the drug molecule once it gets into the or as it -- in getting into the body and then getting out of the body.

So, you know, the major focus of the pharmacokineticist is on the what's called the concentration time profile of drug in the body. So, it is a description of sort of the time dependence of drug exposure in the body.

THE COURT: Do you get into, you know, hardly anybody takes just one drug at a time.

THE WITNESS: Right.

THE COURT: Do you get -- is pharmacokinetics also

concerned with the interaction of various drugs and substances --

THE WITNESS: Yes.

THE COURT: -- in the body?

THE WITNESS: Yes. So, you know, there are issues that arise associated with drug interactions or even food interactions that are associated with how drugs get in the body or how they're metabolized once they get into the body.

So there are drug interactions that are associated with -- with pharmacokinetics of drugs.

BY MR. WONG:

Q. Now, for the other group of students that you teach, the graduate students getting their Ph.D.s, what do they do after they graduate?

A. So, most all of our graduate students, not all of them, but the vast majority of them, will go into the industry. So, you know, go into the industry as formulation scientists or as pharmacokineticists in the industry. There's some fraction of them that will go into academia.

Q. And, generally, what is the subject matter of courses that you teach the graduate students?

A. So, I teach a course in drug stability and drug degradation, kinetics and mechanisms, and occasionally I teach a course in pharmaceutical product development, which introduces the students to the techniques that are used in the

industry to develop pharmaceutical products.
Q. Now, outside the University of Iowa, do you have any affiliations with organizations in the pharmaceutical field?
A. Yes. So, you know, I'm an active member of the National Institute of Pharmaceutical Technology and Education NIPTE.
I also am involved in or have been a member of the American Association of Pharmaceutical Sciences and, also, the Parenteral Drug Association.
Q. What has been your affiliation with the American -- AAPS?
A. AAPS, American Association of Pharmaceutical Scientists? For both the PDA, the Parenteral Drug Association, and AAPS, I've at one time served as the editor of their peer-reviewed scientific journal.
So for PDA, it was the PDA Journal of Science and Technology and for AAPS, it was the AAPS Pharm Sci Tech, which was their journal of applied pharmaceutical science.
Q. And how are those two journals regarded in the field of pharmaceutical technology?
A. They're fairly well regarded.
Q. Do you have your own publications on the research that you performed while at Iowa?
A. Yes. I have 50 or so publications that I have put out, both in my time in the industry and at Iowa.
Q. Now, Dr. Kirsch, have you been an expert witness in a patent case before?

A. Yes, I have.
Q. And in that -- was it a trial?
A. Yes, it was.
Q. And in that trial, what expertise did you offer?
A. I offered expertise in the development of formulations.

MR. WONG: Defendants tender Dr. Kirsch as an expert in the field of pharmaceutical formulation development with an emphasis on drug stability.

MR. O'MALLEY: No objection.

THE COURT: Admitted as such. Thank you.

DIRECT EXAMINATION BY MR. WONG:

Q. Let's get to your opinions, Dr. Kirsch.

Have you reviewed the asserted patents in this case?
A. Yes, I have.
Q. Are the asserted patents shown here on Kirsch 2?
A. Yes, there are four patents that I've considered.
Q. And, in general, what are the four patents about?
A. Well, the four patents are directed to the development of a stable formulation of the antiemetic drug palonosetron.
Q. Have you also reviewed the asserted claims in this litigation?
A. I have.
Q. And are the asserted claims up here on Kirsch 2 now?
A. Yes, that's correct.
Q. Have you identified a representative claim among the

eight asserted claims?
A. Yes. Claim 7 in the '219 patent really contains the elements that are relevant.
Q. And we'll get to each of these elements in a bit, but what is your general opinion regarding each of the components listed here for Claim 7?
A. Well, it's my opinion that these elements are a description or involve the description of a common -- commonly used conditions and components in I.V. formulations that are used for their common uses. So, in my opinion, this patent is invalid because of obviousness.
Q. Now, have you considered who a person of ordinary skill in the art would be with respect to the four patents?
A. Yes, I have.
Q. And who would that person be?
A. The person of ordinary skill in the art, a POSA, would be a formulation scientist typically with a Ph.D. in pharmaceutics or a related field and would have a couple of years of experience in developing I.V. formulations.
Q. Okay. Now, in your opinion, would this POSA have actual experience preparing formulations at the bench?
A. Yes.
Q. And what is the scope of resources that a POSA would draw upon when developing a formulation?
A. Well, a POSA would have their training and background,

their academic training and experience. They would draw on the pharmaceutical science literature, general textbooks.

They would draw upon research articles and abstracts and other sources of information that gave them some idea of the current state of knowledge of palonosetron and related compounds, compounds that had a chemical or therapeutic similarity to palonosetron.

Q. Okay. And in the course of --

THE COURT: And patents, of course.

THE WITNESS: And patents, yes, they would certainly look at patents.

MR. WONG: Thank you.

BY MR. WONG:

Q. In the course of a POSA's practice, would he or she collaborate with others of ordinary skill in the art?

A. Yes, certainly they would. I mean, one of the mechanisms for that interaction, of course, is a project team; but even in the absence of a project team, they would draw upon the knowledge and expertise of clinicians and pharmacologists and other scientists in the field.

Q. So, that would be the same whether the POSA is working in industry or is in academia?

A. Yes, absolutely.

Q. Now, in forming your opinions in this case, what is the relevant date that you tied your opinions to?

A. So, the relevant date is January 30th, 2003.
Q. Okay. And as of January 30th, 2003, how would you describe the field of pharmaceutical formulation development?
A. Well, it was a well-established and well-trodden process by 2000 -- by the beginning of the 21st century. It had been practiced for some decades before, and successfully practiced.
Q. Okay. Let's talk a little bit about how a POSA would develop a pharmaceutical formulation.

Is there a standard formulation development process that a POSA would typically follow in developing a formulation?
A. Yes, there is.
Q. Have you prepared some slides to explain to the Court this process?
A. Yes, I have.
Q. Okay. This is Kirsch Demonstrative 4.

Dr. Kirsch, please explain the product development process that's up on this demonstrative from the standpoint of a formulator.
A. Right. So what I have tried to do in this picture is to describe the formulation development process, which is shown with these green boxes in the context of the overall development process, the clinical trial phase timeline.

And, so, you know, this is a typical -- the typical stages that the formulation scientists work through to develop

the product that's suitable for commercialization and for registration.

Q. We'll go through each of these boxes in a bit, but can you just give a brief overview of each step?

A. Sure.

So, the starting point is typically the product profile, which is really a working document that comes to the formulation scientist. It's typically prepared by clinical and marketing experts and provides sort of boundary conditions in which the formulation scientist is going to work. You know, he's going to -- he's going to help define what that product initially is.

And then -- and that's when the formulation scientist basically gets involved then is in characterizing the drug substance in preformulation studies to determine what sort of technical issues there might be in developing a pharmaceutical product with the product profile that's desired.

And having identified what potential problems there might be, for instance, stability problems or solubility problems that would be relevant for the formulation scientist, then they would go into a design process where they would look at what sort of remedies that they could come up with to overcome these problems.

And then that would ultimately lead them into an optimization process, which would define more specifically

what the actual formulas were that were going to be needed to provide a suitable formulation for commercialization.

THE COURT: When do the excipients come into the picture in your schematic there?

THE WITNESS: Well, they could actually be looked at in some sort of a cursory way in preformulation studies, but more typically, there is a series of screening studies that are conducted in the product design phase to identify those formulation components which may be useful in overcoming whatever issue might appear.

But in addition to that, there's also in the product profile, there will become obvious what some of the formulation components that are going to be needed based on how the product is going to be used.

BY MR. WONG:

Q. Now, when a POSA goes through these steps to develop a formulation, would a POSA have any reasonable expectation of success in this endeavor?

A. The answer is yes. I mean, this is, as I say, a well-studied and well-practiced process, which, you know, in my experience leads to a suitable product.

Q. And in your experience, is that consistent with the formulation teams and projects you worked on at Eli Lilly?

A. That's correct. I mean, I never worked on a project team in which the project was terminated because of a failure to

come up with a suitable formulation.

Q. Okay. So, let's go to the next slide, which is Kirsch 5. And let's start with the product profile. What's involved or what goes into that?

A. So, you know, there are various features that are described as being desirable in this particular -- in a product for a particular compound.

So, you know, there's an identification of what the therapeutic role of that compound is likely to be. There's a description typically of who the patients are that we're going to be treating, you know, what's their condition. Are they geriatric patients? Are they children? Or are they, you know -- whatever.

And then there's typically a description of what dosage forms that is to say do we want to have a capsule? Do we want to have a tablet? Do we have to have a solution? Do we want to have a topical gel? The dosage regimen, which would be how frequently is the drug going to be administered. Is it going to be a single-use administration, or will it be given over a period of time, a course of therapy, for instance?

And then what routes of administration are going to be useful. Will it be useful to have an I.V. formulation, an oral formulation, a topical formulation and so forth. And having, you know, described these desired dosage forms, then that sort of imposes some -- some boundary conditions on what

the formulator is going to need to do, what issues they're going to need to address.

It's also likely that there would be some discussion of what some of the other competitors are in the marketplace.

Q. Okay. Now, if the product --

THE COURT: Similar products, in other words?

THE WITNESS: Yeah, exactly.

BY MR. WONG:

Q. In the case that the product profile defined a solution formulation for I.V. administration, what are the typical formulation parameters that a formulator would need to address?

A. Well, among the most common issues that come up with a solution formulation for I.V. use are issues associated with solubility. You know, can we dissolve enough of it in solution that we can get the appropriate amount into the patient and, also, stability. What will its instability be in a solution medium because drugs are typically more susceptible to drug degradation in solution.

THE COURT: And when you use the term "solution," what are you thinking of, water?

THE WITNESS: Well, you know, typically I.V. formulations are administered in aqueous, in water, solutions. Now, sometimes those solvents are modified with a suitable organic solvent if there's a solubility problem, but typically

it is water.

THE COURT: What's an organic solvent?

THE WITNESS: So like ethanol might be one. So, an alcohol might be one.

THE COURT: It stings.

THE WITNESS: Yeah. Well, I mean, there's sort of a balancing issue, you know.

In addition to that, for an I.V. solution formulation, solubility and stability I've mentioned. Because it is going to be administered intravenously, it has to be sterile, so, you know, that puts certain boundary conditions on the formulator.

It has to be isotonic, so that also puts a requirement on the formulation.

BY MR. WONG:

Q. Now, is the formulator involved or does the formulator have input in this product profile definition?

A. This is -- usually comes to them as the requirements of the desired product or the features of the desired product.

Q. Okay.

THE COURT: Can they balk and say you're asking for something that you need to think through again?

THE WITNESS: Well, certainly there can be a discussion when they have some basis on which to -- on which to, you know, discuss the matter.

So, you know, typically the product profile comes to you, and then you begin to investigate whether, you know, what the technical issues might be in actually achieving what's desired.

And this is a living document. So, you know, there are changes that are made, adaptations that are made.

BY MR. WONG:

Q. So what happens next in the process?

A. So, the next step in the process is the preformulation studies, and, basically, these studies are intended to identify what the critical issues that the formulator is going to face, I mean, what are the major problems that they are going to need to overcome.

And for a solution formulation, certainly among the major problems that they're likely to encounter are issues of solubility, is it -- can you get enough of it into solution, and frequently that is the biggest problem.

And then, secondly, stability. So, in the preformulation studies, they would conduct stability screening studies to try to identify the major degradation processes that were involved in destabilizing or degrading the drug substance.

They would look at a variety of stress conditions, high pH, low pH, so alkaline and acidic conditions. They would look at photolytic, you know, whether or not light tends to

degrade the compound.

They would look at oxidation and whether or not the compound is susceptible to oxidative stress.

THE COURT: Temperatures, also?

THE WITNESS: Absolutely. Thermal stress, as well.

BY MR. WONG:

Q. For a POSA in 2003, were preformulation studies routine?

A. Yes, they were.

Q. Are preformulation studies a requisite step in developing a formulation for any molecule?

A. Yes. You need to know what the technical issues are likely to be or are with regard to putting the API in the desired dosage form.

Q. And, in general, what would the expectation of a POSA be regarding the stability for any molecule in solution?

A. Well, the formulator is going to go into these studies, assuming that there is an instability associated with the compound. I mean, they are not allowed to simply say that, well, I believe the compound is stable, and, therefore, I'm not going to look at it.

I mean, you have to prove positively that the compound is stable or not stable and, in general, what are the major degradation processes that are associated with the compound.

Q. So, after performing the preformulation studies, what does a POSA know?

A. So, a POSA would know, you know, what the major technical issues are, and then a POSA could rely on, you know, what's known in the art, what's known in the science of formulation development to remedy those problems.

And they would take that knowledge, the combination of that knowledge, into the product design phase and look to see what remedies may be useful to overcome whatever problems that they've encountered. So --

Q. Sorry. Before we get to the product design phase, would a POSA need to determine the exact mechanism of degradation before moving forward?

A. No. In my experience, the mechanisms of degradation, which, you know, have to do, for instance, with how electrons move in a molecule to generate a new chemical entity, that type -- that level of knowledge is not typically the result or not ever the result of preformulation studies. That type of knowledge comes much later on, if ever.

I mean, there are compounds that have been around for decades where the mechanisms of degradation are still under study. Compounds like aspirin under some conditions, the mechanisms of degradation are still a matter of research activity, or penicillin is another one where the mechanisms of degradation have been studied for many years.

And, you know, that's, basically, some of the work that I do in my laboratory. But in terms of the formulation

development process, what the formulator needs to know, you know, what are the major degradation processes, and that will help him identify what the usual and useful remedies may be for overcoming those problems.

Q. Okay. And were there any standard textbooks that taught a POSA the usual remedies for the different degradation pathways?

A. Oh, yes. I mean, there are many references. I list a few, make reference to a few year, but, you know, this is a pretty good one, a book by Wells published in 1988, which describes preformulation processes and the usefulness of the preformulation information.

Q. Okay. So, for the record, this is DTX-0349. We're at Page 44.

So, what is described here in Table 5.17?

A. Right. So this excerpt from this textbook is, you know, the type of information that one would find in standard references. This describes simple strategies for improving drug stability, and it says, you know, if we know what the degradation process is, then there are a variety of methods of protection, a variety of remedies that we might use for hydrolytic degradation, for susceptibility to thermal stress, to oxidation, to photolytic degradation.

So it gives, you know, a pretty good guidance in terms of what the formulator is -- needs to consider.

Q. And if the preformulation results show that oxidation was a pathway for drug instability, what does Wells disclose as the remedies here?

A. So, Wells discloses, basically, four suggestions: You know, the removal of oxygen or the removal of air; pH adjustment as a means of controlling oxidation; the use of an antioxidant; or the use of chelating agents, such as EDTA.

Q. So, what happens next after the preformulation information is obtained?

A. So, at that point, you know, the formulation scientist has an idea of what the potential technical issues are in creating a useful formulation, and then they begin to screen the remedies, which, you know, are a combination of the conditions and the excipients that may be useful in overcoming whatever problems that they have identified.

So -- and they would also screen potential packaging components to see whether or not there's any issues associated with those.

So, what they're going to do is to conduct a bunch of -- a series of screening studies to look to see what remedies might be useful in overcoming the problem, and then based on those studies, they're going to be able to select, at least identify, you know, what the ingredients may need to be in the formulation and what sort of packaging system is going to be most appropriate.

Q. For a POSA in 2003, was it routine to conduct screening studies?

A. Yes.

Q. So, what happens next after the product design is complete?

A. So, again, at this point, the formulator has a pretty good idea of what is likely to be in the product and how the product is likely to be packaged; but the exact amounts, the ingredients, the concentrations of the ingredients still need to be defined in detail.

So, at that point, the formulation scientist would conduct optimization studies to focus in on what the exact combination and concentrations need to be. That would lead to a unit formula that described the formulation and the ranges that are associated with those components, the specifications that are needed.

Q. How would a POSA conduct formulation optimization experiments?

A. Well, the typical way, and it has been the way for some numbers of decades, is to use a design-of-experiments approach, which is a -- a method of efficiently conducting studies to lead to an optimization, to lead to an optimized formulation.

And, you know, this was well practiced in the '80s and '90s and beyond and would efficiently, again, lead the

formulator to obtain a final formulation.

Q. Are there any standard tools to help a POSA conduct these design-of-experiment studies?

A. Yes, there are. I mean, there are a number of software tools that will generate experimental protocols that the formulator could then use and also assist in the analysis of -- the statistical analysis of the data to arrive at an optimized formulation.

Q. Okay. Did you have experience at Lilly conducting -- using software packages to conduct the experiments?

A. Right. So when I joined Lilly in 1982, one of the very first things that they did was to have me enroll and take a course in statistical design of experiments and optimization of formulations using statistical design of experiments. That was my initial training when I joined as an industrial scientist.

THE COURT: So, you had to learn how to create the software, in effect?

THE WITNESS: No, how to use the software. I mean, the software that we used at Lilly was SAS software, and there are any number of packages that are available. So it's really a matter of knowing how to use the tools that are made available.

THE COURT: Can you just, you know, like when somebody uses TurboTax® to do their tax return, that's a

software package.

THE WITNESS: Sure.

THE COURT: It's got a lot of information already in it that tells you where to plug in your information, and then it runs and gives you the finished product.

That's a clumsy example, but what would SAS provide and what would the scientists using SAS provide in the simplest sense?

THE WITNESS: Okay. So, let's suppose that the formulator decides that there are a couple of ingredients that -- a couple of excipients that might be useful. Then what the formulator would do would be to make a decision about what concentration ranges, for example, might bracket the region that they want to -- they want to investigate.

And they could go to one of these software packages, and they would basically input the variables, that is, the excipients, and they would also include the concentration range that they were interested in.

THE COURT: And the API or not?

THE WITNESS: If the API is a variable in this experiment. So, for instance, if concentration of the API is a critical characteristic that they've identified, then that could certainly be a consideration, as well, or part of the program.

And then what the software will do will be to generate

experimental protocols that basically describe for the formulator what combinations of each excipient they need to -- they need to put together to study what's called the design space; that is, the range of concentrations and the combinations of excipients that they're interested in. So the experimental protocol basically that they're going to follow is then output for them.

Then they need to take that experimental protocol and actually conduct the studies which might be, you know, looking at changes in drug potency over some period of time. They would get results; for instance, a decrease in drug potency, for each experimental condition.

They would input that into the program, and then the program would do the computations that were necessary to arrive at an optimized formulation. Now, there's a lot of input that the formulator has in terms of design, selecting the right experimental design and the right range of conditions and then conducting the experiment, so it's --

THE COURT: So, and like any other software thing, it could be done by hand.

THE WITNESS: Yes.

THE COURT: But the software just contains information that's sort of standard, and also it's faster than going through the variables one by one.

THE WITNESS: Right. Well, I mean, there's certainly

a big advantage in this kind of methodology over looking at each excipient one by one, because in this experimental -- in this approach, you can look at the interaction between excipients. So, you know, if there's a positive -- if there's an interactive effect, you can also investigate that.

But you're right. I mean, it simplifies a lot of the computations that are necessary. When I was trained in design of experiments, the first way we went through it was by hand so that we understood, you know, what the computer program was actually doing, and we went through all the calculations by hand. I mean, that can be a little tedious. It is easier to do with a computer.

THE COURT: Okay.

BY MR. WONG:

Q. Now, were you in court on Tuesday, I believe, to hear Dr. Calderari's testimony?

A. Yes, I was.

Q. And how did he characterize the optimization studies carried out for palonosetron at Syntex?

A. Well, I mean, he characterized it as a -- sort of a computerized simulation process that was very high tech; but as I said, this was not, you know, high tech in the 1980s. This was the standard operating procedure for formulation scientists.

And, actually, if you go into other manufacturing

industries, these techniques had been around since the 1950s. So, you know, this is not, you know -- this is not new, advanced kind of technology.

Q. For a POSA in 2003, were the experiments required in product optimization routine?

A. Yes.

Q. Okay. Okay. What are the other performance attributes of the optimized I.V. formulation that a POSA would have to consider?

A. So, you know, as I mentioned for I.V. formulations, there are considerations in terms of the sterility, and they would need to select a pH within some range of pHs that was going to be compatible with an injection directly into the vein, and they would also need to consider isotonicity as a consideration again for patient comfort.

Q. Okay.

THE COURT: In your experience, Doctor -- I don't know anything about pH except what I learn in the evidence in this case. In other words, even if I did know something about it, I wouldn't expert my extrajudicial knowledge into what I'm learning from the evidence here, but I think I've heard that the body's pH is 7.4?

THE WITNESS: That's correct, for the most part, yes.

THE COURT: I mean, I've heard it in the evidence so far this week.

THE WITNESS: Uh-huh.

THE COURT: And you just said that pH has at least two aspects. One is you need it to be compatible with injecting it into the human body. It's also related to stability of the formulation, right?

THE WITNESS: That's correct, yes.

THE COURT: Okay. So, in terms of the former, the injecting into the human body, is there a standard range outside of which you wouldn't want any I.V. formulation to fall?

THE WITNESS: Well, there's a standard range which is considered acceptable, but there are exceptions to that range, as well. So, typically in the pH range of about 4 to 8, pH 4 to pH 8, that's usually considered acceptable for injectable products.

I mean, what you have to remember is that, you know, compared to the volume of blood in the body, you're injecting a small volume of the drug solution, and the body has a substantial buffering capacity, has a substantial ability to take in whatever acidity is associated with that solution and neutralize it, essentially, to bring it to pH 7.4. So, you know, typically there's really not an issue with having a pH somewhere in the 4 to 8 range.

THE COURT: Okay.

THE WITNESS: There are some drug products where,

typically because of solubility issues, they need to have pHs in excess of that range, and, you know, there can be some issues in terms of the comfort of injection in those situations.

BY MR. WONG:

Q. Okay. For pH and for a POSA as of 2003, was it routine practice for a POSA to adjust the formulation of a pH to an optimal pH?

A. Yes.

Q. And for sterility as of 2003, were there routine practices that a POSA could follow to make an I.V. solution sterile?

A. Yes.

Q. And tonicity, why is it important to make an I.V. solution isotonic?

A. Well, again, it becomes a patient comfort issue. You don't want the injection to be irritating. You don't want to cause hemolysis to have blood vessels -- or not blood vessels, but red blood cells rupture because of a hypotonic or a low tonicity solution.

So, you know, it was very common to -- it is still very common to try to ensure that the solution has a tonicity usually measured in terms of what's called osmolality that's within an acceptable range, compatible range for injectable use.

Q. Okay. For a POSA in 2003, was it routine -- were there routine practices for making an I.V. solution isotonic?

A. Yes. I mean, it is a very simple process. I mean, basically, what's done is to measure the contribution that various -- the various needed excipients in active ingredient contribute to the tonicity of the solution and then to add an additional tonicity-modifying agent to bring that solution to what's called an isoosmotic or an isotonic condition. And there's a range of osmolality that the formulator aims for.

Q. Okay. Let's wrap up this formulation tutorial.

Have you prepared a slide that shows what sort of resources were available to a POSA to assist in this formulation development process?

A. Yes. So, you know, again, the formulator is going to rely on their training and their background, but in addition to that, there is a large number of basic reference sources that are available to the POSA, both in terms of textbooks and also in terms of review articles.

You know, I'm sure that there are at least 30 textbooks out there that deal with the formulation process with preformulation and formulation development, and we've pointed to a few of those which I think are pretty good, the Wells book of 1998(sic), this Swarbrick book of 2000, and, actually, an article within this book by Broadhead, which is relevant to injectable drug formulations.

And these would tend to inform the formulator about, you know, common formulation strategies and the accepted pH range and stabilizers that may be useful and tonicity-modifying agents, common buffers, the volumes that are appropriate and would guide them in terms of the stability protocols that they need to follow. So --

THE COURT: How do you define "buffer"? Not technically, but what do you think of when you say the word "buffer"?

THE WITNESS: So, a buffer is a substance which resists a change in pH. So it's typically the combination of a weak acid and a base which resists a change in pH.

THE COURT: So, buffer connotes controlling pH.

THE WITNESS: Yes.

MR. WONG: And for the record, this is Kirsch Demonstrative 11, and we're looking at Wells 1998, which is DTX-0349, Swarbrick 2000, which is DTX-0235, and Broadhead 2001, which is DTX-0271?

MR. O'MALLEY: And just minor, to correct the record, we're just looking at pictures of their covers.

THE COURT: Right.

MR. WONG: Your Honor, I'm going to shift topics now. I think we have taken --

THE COURT: If you want to offer excerpts --

MR. WONG: Sure.

THE COURT: -- from behind the covers of those, you should confer later and then make your offer.

MR. WONG: And we will. And we're going to review excerpts in the rest of the slides.

THE COURT: Okay.

MR. WONG: I'm about to move topics. Is it a good time to take a break?

THE COURT: Good time for a break, yes.

MR. WONG: Thank you.

THE COURT: This is your first time on the stand here. Watch your step as you get down.

(Brief Recess.)

THE COURT: Back in session.

MR. WONG: Thank you.

BY MR. WONG:

Q. So, Dr. Kirsch, while we're on this slide, and just for the record, let's review some of the excerpts from these standard formulation textbooks.

So first let's take a look at the Wells textbook, 1988, Page 16. So, for the record, this is an excerpt from DTX-0349 on Page 16.

Dr. Kirsch, what's disclosed here in Section 5.4?

A. Well, in this section, Wells is pointing out the importance of pH, and, in particular, pH extremes, and the instability of drug substances and solution. And so he's made

the observation that many drugs are stable in the region of 4 to 8, that for many drugs, this is the optimum pH stability, somewhere in that range.

THE COURT: That's exactly what we were talking about before. And it even cites the, what's called homeostatic pH of 7.4 which would be the person -- the human? See the next sentence?

THE WITNESS: Right, right. He goes -- that's correct. He goes on to say, and this is maybe a matter of serendipity, but that also is the pH range where -- where the blood can accommodate the pH due to a neutral pH.

BY MR. WONG:

Q. Let's stay with Wells 1988. And let's look at an excerpt on Page 26.

THE COURT: You just said neutral pH?

THE WITNESS: Well, close to neutral. 7.4 is a little bit -- little bit higher than neutral. Neutral is considered 7, pH 7.

BY MR. WONG:

Q. So, for the record, this is an excerpt from DTX-0349 at 26. And, Dr. Kirsch, what does Wells 1988 disclose here in Section 5.8?

A. Well, in this section, Wells is pointing to some potentially useful chelating agents which are known in the art to assist in certain stability circumstances, for instance, in

certain oxidative degradation, and points to well-known chelating agents. And, in particular, you can see that -- that he's pointing to EDTA as a particularly effective pharmaceutical chelating agent.

Q. Let's go to another textbook, Broadhead 2001, and let's look at an excerpt from Page 5. Dr. Kirsch, what does Broadhead 2001 disclose here on tonicity?

A. So, Dr. Broadhead had contributed a chapter in this book dealing with the development of injectable drug products and addresses many of the issues that we've mentioned earlier, including the issue of tonicity, and here, she's pointing to the osmolarity range, that 280 to 290, which is associated with isotonicity.

And she also points to a few of the commonly used excipients that are used to adjust a formulation to tonicity, for example, mannitol and dextrose and other excipients, and, you know, these are particularly useful, as she points out, in situations where sodium chloride may have an adverse effect on some attribute of the formulation.

Q. Okay. Let's go to Broadhead, Page 5 again, the next slide. And what is disclosed here in these excerpts from Broadhead?

A. So, in this section, she's talking about the types of buffers again that are used in injectable formulations and is talking about a phosphate as one of those but also lists as

some other common buffering agents used in parenteral injectable drug products. Among them is a citrate, and there are a number of others listed as well.

Q. In the highlighted section, does Dr. Broadhead also list the common buffer concentrations that could be used in formulations?

A. Right. Again, so, you know, there is a desire not to add excess buffer so as to cause any problems with -- with pH upon injection if the buffer is not exactly at 7.4, so, you know, there's a recommendation to use 10 to a hundred millimolar range as a suitable range for buffers.

Q. Okay. And, lastly, let's go back to Broadhead, Page 3. What does Dr. Broadhead disclose here about volumes of injectable formulations?

A. Right. So she's pointing to the definition of a small volume parenteral. An SVP is a small volume parenteral. And according to the U.S. Pharmacopeia, a small volume parenteral is a product that contains less than a hundred mLs of solution.

THE COURT: So 5 mLs, 5 milliliters? 5 milliliters?

THE WITNESS: Yes, 5 milliliters.

THE COURT: Would be a vial?

THE WITNESS: 5 milliliters would be a small volume parenteral. So anything less than a hundred mLs is considered small volume parenteral, as distinguished from what she calls

LVPs, which are large volume parenterals, you know, which are typically the, you know, the liter bag of D5W or some other, you know, some other solvent that's slowly dripped into the patient.

BY MR. WONG:

Q. Okay. In addition to the routine formulation development activities and textbooks we just reviewed, what else would a POSA consider in developing an I.V. formulation?

A. So, of course, as we mentioned before, their training and their expertise, but they would also look to the available literature, the public literature that dealt with palonosetron and related compounds, therapeutically- and chemically-related compounds. So they would look to whatever is published that would inform them and would assist them in the design and development of their desired injectable formulation.

Q. Have you reviewed the relevant literature that a POSA would have considered with regard to developing palonosetron formulation?

A. Yes. So this was the, you know, the first thing that I did when I got involved in this -- in this situation, was to attempt to put myself in the position of a POSA as of 2003 and to do a search through the literature to see what -- what I found that -- that I thought would be relevant to a POSA.

Q. And for the record, did you only rely on publicly available documents of prior art in forming your opinions on

obviousness?
A. Yes.
Q. Have you prepared a slide that reviews the relevant prior art that a POSA would have uncovered?
A. Yeah, I put together a timeline that shows the publication dates of various documents and information that a POSA would likely use in helping them -- helping to inform them about what they need to do in the formulation development process.
Q. Okay. And we'll cover these individually as we move forward, but how would you characterize the prior art relevant to palonosetron prior to the filing date?
A. Well, there was quite a bit of information that was available in various forms that described palonosetron.
Q. Okay. And would these be -- would these references, these prior art, be helpful to a POSA in developing a palonosetron formulation?
A. Yes.
Q. So what is the first piece of prior art we'll review?
A. So, the first piece of art is the -- the product patent, the three -- what's called here the '333 patent published in 1993.
MR. WONG: Okay. And for the record, we're looking here at an excerpt of DTX-0343 on Page 1.
BY MR. WONG:

Q. You mentioned that the '333 patent was published in 1993. Who was the assignee of the '333 patent?

A. So, this was a patent that was generated by Syntex, the Syntex Research Group.

Q. And, in general, what does the '333 patent disclose to a POSA?

A. So the '333 patent is again a compound patent that describes an entire class of compounds of related -- chemically-related compounds which also they discuss some of their pharmacological properties as well, but, in particular, they describe the chemical structure of the -- of palonosetron in this -- in this patent.

Q. Let's go to the next slide. This is pages from DTX-0343 at 2 and 4.

Dr. Kirsch, what is disclosed here?

A. So, you know, this gives the general formula for the compounds that they disclose in the patent and then goes on to describe, you know, what chemical features at each of these positions -- R3, R2, and R1, that make up the chemical formulation of what later became known as palonosetron.

THE COURT: This chemical drawing that contains what you just said, R1, R2, and R3, as well as some actual chemical names, oxygen, right, nitrogen?

THE WITNESS: Right. So --

THE COURT: So R1, 2 and 3 are variables; is that

right?

THE WITNESS: That's correct.

THE COURT: Okay.

BY MR. WONG:

Q. So what does this next slide show, on Kirsch 13?

A. So this is the chemical structure, the assembled chemical structure of palonosetron, and also identifies that the -- the number that they gave it as part of the series. So the RS-26259 is the -- is the compound number for palonosetron that they refer to in the patent.

Q. Okay. And is the structure of palonosetron itself -- strike that.

The structure of palonosetron, would that be important to a POSA?

A. The formulator is definitely going to look at the structure because it will inform him, as a starting point, about potential issues with solubility. He can make some predictions about solubility based on structure. And, also, he will look at that structure to see whether or not there are particular types of structures in it, what we call moieties in it, which have the potential to undergo chemical instability.

THE COURT: What is the -- just out of curiosity, there is a two-letter abbreviation that's just sitting in the space there.

THE WITNESS: Right here?

THE COURT: Yeah. What is that, please?

THE WITNESS: So, this particular form of palonosetron is what's called the hydrochloride salt. So, basically, this is part of the structure in that it is -- it is the part of hydrochloride, so the hydrochloride is this proton here, HCl, and so this is the salt form. This is just the chlorine that goes with the HCl.

THE COURT: What are the two letters there?

THE WITNESS: This is Cl.

THE COURT: With some kind of a symbol after it?

THE WITNESS: A negative sign, so it has a negative charge on it, whereas this function up here has a positive charge.

THE COURT: And the Cl is just an abbreviation for a little chemical structure that's not depicted there?

THE WITNESS: It is the symbol for an atom, a chlorine atom.

THE COURT: So you don't have the atom drawn there; everybody knows that that's the chlorine atom?

THE WITNESS: Right, so --

THE COURT: It is attached to the -- to the palonosetron molecule, right?

THE WITNESS: Right. It would be part of the crystalline structure of the molecule in the solid state. As soon as we put it into an aqueous solution, then this chloride

would separate from the rest of this structure and just kind of float around. You know, sort of like if you think of sodium chloride, you know, when we put salt in the solution and the two parts of it kind of dissolve away and separate.

BY MR. WONG:

Q. What, in particular, would be relevant to a POSA about the structure of palonosetron in terms of potential instability?

A. So, one of the features that they would likely observe is this, what's called quinuclidine ring which contains a --

THE COURT: Could you spell that word? I don't --

THE WITNESS: I don't know if I can spell it. Let's see. Q-U-I-N-U-C-L-I-D-I-N-E maybe, quinuclidine.

THE COURT: And it's the one with the jagged line through it?

THE WITNESS: That's right. This is -- this is a ring structure and they're describing all -- each intersection there is a carbon atom, and then up here at the top is a nitrogen atom, and that nitrogen atom has three bonds that go to it, so we call that a tertiary amine. And this particular structure, I mean, tertiary amines and really amines in general, are potentially susceptible to oxidative degradation. So a POSA formulator would look at that and potentially wonder whether or not there was some potential for oxidation.

BY MR. WONG:

Q. Do all tertiary -- or do all structures with tertiary amines degrade by oxidation?
A. No. They don't all degrade. That just gives an indication of a possible degradation pathway, not a -- it doesn't necessarily occur.
Q. The fact that all tertiary amines do not degrade, would that structure still be relevant to a POSA formulating palonosetron?
A. Yes. It would alert them for the possibility of oxidative degradation.
Q. Okay. If a POSA saw the structure of palonosetron as disclosed in the '333 patent, what would a POSA suspect? What the POSA understand from this structure?
A. Well, again, the POSA would glean from the structure information relevant to the solubility and also potentially to instability, to some possible instability pathways.
Q. Let's go to the next slide.
THE COURT: Could I just ask you, solubility, to a chemist --
THE WITNESS: Um-hum.
THE COURT: -- if I've got sugar, put it in the water, stir it up, with any luck I'll get it to dissolve, right?
THE WITNESS: (Nods head.)
THE COURT: It's dissolved.

THE WITNESS: That's correct.

THE COURT: It's still in there, you can taste it.

THE WITNESS: That's correct.

THE COURT: So what does solubility refer to, when a chemist talks about that?

THE WITNESS: Right. So, solubility, you know, refers to the -- the state of the molecule in the solution, so the undissolved part of that sugar is still in its solid form, it's still in its solid state, but if the -- if the conditions are right, molecules of that sugar will be completely surrounded by solvent and will dissociate from one another so there's not two sugar molecules together, they are surrounded and enclosed by solvent, and so they sort of move freely in the solution.

THE COURT: That grain of sugar that I could see in the spoon is more than one molecule of sugar?

THE WITNESS: That's correct.

THE COURT: And so when that grain of sugar goes into the water, those molecules fall apart?

THE WITNESS: The molecules separate from one another --

THE COURT: They separate.

THE WITNESS: -- from one another, correct.

THE COURT: Okay. Thank you.

THE WITNESS: Um-hum.

BY MR. WONG:

Q. Next slide, we're looking at an except from DTX-0343 at Page 6.

Dr. Kirsch, what is disclosed here on Page 6?

A. So, also in the patent, the patentees describe some of the potential utility of these compounds, and they particularly comment on their potential use in preventing emesis from various sources, radiation poisoning and radiation therapy, and they also point to its potential use as -- in preventing chemotherapy-induced emesis, or CINV, as we've been referring to it here.

Q. Let's go to Page 16 which is on the next slide, an excerpt.

Dr. Kirsch, what is disclosed here in the '333 patent?

A. So, the patentees suggest some various formulations that may be useful or at least the general description of some formulations that may -- that may be useful, and they point to the suggestion of an intravenous formulation and, you know, they give some sort of boilerplate suggestions as to what that might be composed of.

Q. Does the '333 patent disclose anything else about how palonosetron could be administered?

THE COURT: Compound of Formula I.

THE WITNESS: Right here.

THE COURT: Yes. I see that. But we looked at this

big, you said, class drawing.

THE WITNESS: That's right.

THE COURT: But then we looked also at the palonosetron composition, right?

THE WITNESS: Um-hum.

THE COURT: How do we know that we're not talking about the whole class there, that we're talking about RS-252 -- whatever that number was?

THE WITNESS: Right. And I think the answer is that they are referring to the whole class there.

THE COURT: Okay.

THE WITNESS: They are referring to compounds of Formula I and not specifically to palonosetron.

THE COURT: Thank you.

BY MR. WONG:

Q. Does the '333 patent disclose anything else about how compounds like palonosetron could be administered?

A. Well, it also makes reference to their potential use as single-use-dosage forms, so, as opposed to, you know, a long-term therapy, so they also suggested it could be administered as a single-use-dosage form.

Q. And, for the record, this is Page 8 of DTX-0343.

Dr. Kirsch, did Syntex ever publish any scientific articles related to palonosetron?

A. Right. So the patentees here actually, the primary --

the authors of that patent and also some other of their colleagues also went on to publish their results in a peer-reviewed journal, *The Journal of Medicinal Chemistry*.

Q. And, for the record, this is DTX-0282, we're looking at Page 1.

What year was -- I'm going to refer to this as Clark 1993. Is that okay?

A. Yes.

Q. What year was Clark 1993 published?

A. So the Clark article came out in 1993.

Q. And, in general, what does Clark disclose?

A. So, again, the Clark article is -- has a lot of the same information that the patent has. It discusses this series of compounds that they've discovered. It describes them chemically and also describes some of their pharmacological activity that they've -- that they've investigated.

Q. Okay. Let's look at the abstract which is on Page 1.

And, Dr. Kirsch, what does Clark, et al., conclude in their abstract?

A. So, in their abstract, they make particular reference to palonosetron, and here, they identify it as (*S*,*S*)-37 so you can see it appears a couple of times as (*S*,*S*)-37, that's the shorthand that they use, but this chemical structure here is palonosetron.

And they, you know, commented on its high affinity for

receptors, which sort of suggests their potency, and that is a highly potent compound, and they also comment that in some of the animal models where they looked at its activity, that, again (*S*,*S*)-37, palonosetron, was the most active of the groups of -- of the group of agents that they looked at and, in particular, in blocking cisplatin-induced emesis in two animals, in the ferret animal model and in the dog model. And the cisplatin-induced emesis is a form of CINV.

THE COURT: So, referring to the actual blocking of the 5-HT_3 receptor, they do some studies before they go into animal studies where they can tell that the 5-HT_3 receptor is being effective?

THE WITNESS: That's correct. They did binding studies to see what -- you know, how -- basically, what the affinity for the various molecules was to this particular receptor.

THE COURT: How do you get the receptor?

THE WITNESS: Well, to be honest with you, that's not really my area of expertise, so --

THE COURT: They got tissues though?

THE WITNESS: Yeah.

THE COURT: They got tissues --

THE WITNESS: But they have to isolate the --

THE COURT: And they go into the lab with the tissues, right?

THE WITNESS: Yeah.

THE COURT: Okay.

BY MR. WONG:

Q. Dr. Kirsch, does Clark 1993 disclose anything else that would be relevant to a POSA formulating palonosetron?

A. Well, they compared a whole series of compounds, so, you know, there are related compounds that are discussed in the -- in the Clark article that are therapeutically related to palonosetron. And one of the compounds that they point to is this compound RG 191 -- 12915, which was under development by Rhône-Poulenc at that time. And what they pointed to was -- was, you know, the therapeutic similarities and the fact that it's of the same class of drugs, but then they also described some relevant structural similarities between -- between 12915 and palonosetron, and they point in particular to the confirmation of this quinuclidine -- there it is, spelled out for us -- quinuclidine ring.

THE COURT: But this particular RG 12915 that they're talking about is not within the compounds claimed in the '333 patent?

THE WITNESS: That's correct.

BY MR. WONG:

Q. For the record, this is Page 5 of DTX-282.

And how does RG 12915 compare to palonosetron?

A. So, we can look at the two structures together, and, you

know, there are some structural features that are similar. There's a benzene ring that's contained in both. There's what we call an amide that's contained in both. This is -- this is a structure here that's called an amide, and we'd also see it in -- I should say that this is palonosetron and this is the Rhône-Poulenc compound.

And then, notably, they also see the quinuclidine ring in both of those structures.

Q. Does it make sense that Clark 1993 compared the structures of these two compounds?

A. Well, again, for the purposes of Clark, they were therapeutically-related compounds, so, you know, to the extent that they're investigating structure-activity relationships, relationship between structure and their pharmacological activity, then, yeah, it would absolutely make sense.

To a formulator, a POSA, what they're looking at is they're looking at whatever information they can glean about related compounds, compounds that are related to palonosetron that may inform them about their efforts to develop a stable palonosetron formulation.

Q. Okay. Was there anything else in the prior art that was published specifically about RG 12915?

A. Yes. There was another study that was conducted by -- by pharmaceutical, more formulation types of scientists, and was published in the *International Journal of Pharmaceutics* that

discussed RG 12915.

THE COURT: What year is that, can you tell?

THE WITNESS: Yes. Yes, Your Honor. The year is 1995. We've shown it up here, and -- we refer to this as Won 1995, so --

THE COURT: Looks like Dr. Tang is in there, too. But it's called Won because Won gets the first listing?

THE WITNESS: You know, I don't know that that's the same Dr. Tang.

THE COURT: Okay. Never mind.

But I did want to ask, this RG 12915, is it equivalent to any of the marketed competitor drugs?

THE WITNESS: I don't believe that this one was taken to market.

THE COURT: Okay.

BY MR. WONG:

Q. For the record, we're looking at DTX-0345, Page 1. So what is the title of Won 1995?

A. So this manuscript would have been very informative to a POSA working on palonosetron or related compounds because it contained information about the potential chemical instability of these compounds. In particular, it looked at photolytic, that is, you know, the degradation that occurs on exposure to light, and oxidative degradation of this compound.

Q. Okay. And what does Won 1995 disclose about the possible

degradation of RG 12915?

A. So, they found significant evidence of both photolytic and degradative -- or oxidative degradation that occurred with this compound, and, you know, this is their starting material, this is the 12915. They found photolytic degradation which they described simply here, and then they describe some general pathways by which oxidative degradation may have occurred, so, basically, what they did was to identify some of the degradation products that occurred, and among those degradation products was degradation at this quinuclidine ring, this is the N-oxide form, in which oxygen adds to the tertiary amine of the quinuclidine ring.

Q. And, for the record, this is on Page 2 of Won.

Does Won disclose any remedies to address the oxidative degradation that is reported here?

A. So, in addition to identifying degradation pathways, they also went on to study some of the remedies that might be useful, some of the conditions and excipients that might be useful in overcoming the oxidative instability of this compound.

Q. Let's go to the first remedy. This is Page 8 of Won. Dr. Kirsch, what is disclosed here?

A. So, what we've excerpted from this article is this figure, which is relevant. What this figure does is it shows the potency, that is to say, the percent of the active

ingredient, the concentration of the active ingredient, as a function of time. In general, you see this decrease in potency with time, which is an indication of chemical instability.

And what they did in this particular study was they looked at how starting with different concentrations of the active ingredient affects how fast and the extent to which degradation occurs. And their finding was that, at the lowest concentration, at this concentration, the compound appeared to be the most stable in solution. So this informs the POSA formulator that a concentration of the active may play a role in these types of oxidative processes.

Q. Okay. Does Won look at any other remedies for addressing instability?

A. Yes. As is very typical in these studies, they also looked at the effects of pH, so once again, we have the same kind of plot, potency as a function of time, and they studied the instability process, the oxidative instability process, under a range of pHs, and found some pHs gave rise to a much more rapid rate of degradation than others.

And so, again, informing the POSA of that pH is likely to be an important player, and in this case, the pH of 6.8 was -- you know, looked to be the best, at least in these three conditions that they looked at.

Q. Okay. Does Won 1995 disclose any other remedies that

might be helpful to address the instability of RG 12915?
A. So, they did, and they also looked at how EDTA may be useful in stabilizing this compound against oxidative degradation. So, again, we see a concentration versus time profile. They showed that EDTA, which they point to as being by far the most common chelating agent used, had a profound effect on oxidative degradation in that the solutions with the presence of EDTA essentially didn't show any degradation.
Q. So a POSA considering the Won 1995 article, how would that POSA interpret the disclosure here, in terms of formulating palonosetron?
A. So, it would -- it would alert them to the possibility of oxidative degradation at the quinuclidine ring, which these two compounds have in common. It would point them to some potential remedies that were worth exploring, the concentration of the active substance, the active drug, pH, and also potential utility of a chelating agent to overcome oxidative instability.
Q. Okay. Let's get back to the palonosetron articles.
Did Syntex publish any other articles regarding palonosetron that would have been relevant to a POSA?
A. Yes. So, part of the same group that did the '333 patent also published some pharmacological characterization of palonosetron, and here it's called 25259. Remember, this is the compound number for palonosetron. And so, in this paper,

the pharmacologists and also with some chemists looked at the pharmacological properties of palonosetron in particular.

Q. Okay. For the record, this is DTX-0283, Page 1.

So what does Eglen 1995 disclose to a POSA?

A. So what a formulator POSA would get out of Eglen '95 was some sense of the potency or the potential potency of palonosetron and, quite relevantly, in comparison to some other compounds of known potency.

So, in this study, for instance, they looked at the potency of palonosetron as by intravenous administration, and they commented that the -- that the potency of palonosetron was three times greater than granisetron which -- in which the active dose was already known, and 55 fold more potent than ondansetron, again, a compound for which there was information that a POSA could use for the actual dosage. So this would help them to understand what kinds -- what the range of doses might be for palonosetron.

Q. Okay. And this is Page 5 of Eglen 1995.

Let's go to Page 6. And what is disclosed here, Dr. Kirsch, in Eglen 1995?

A. Well, again, they comment on the potential for palonosetron administered intravenously to inhibit CINV in the models that they use which was the ferret and dog model.

Q. And so is it fair to say that Eglen 1995 was a preclinical paper? Preclinical --

A. That is correct. That's correct, it's a preclinical paper.

Q. Was there anything else in the prior art that actually disclosed palonosetron when administered to humans?

A. There were a few papers that deal with the Phase I and a few that deal with Phase II studies that were also reported in the prior art. And there were a couple of abstracts that described some of the features of the Phase I studies conducted by Piraccini that appeared in the -- in the prior art. And, you know, these also had some utility for -- for a formulator.

Q. Okay. Let's take a look at the top excerpt. This is an abstract DTX-0272, Page 3, from the American Society of Clinical Oncology in 2001. Dr. Kirsch, what is the relevance here to a POSA?

A. Well, here, the POSA is informed that some of the pharmacokinetic properties of palonosetron, in particular that it has a very long half-life, so it stays in the body for -- for a long period of time, and, you know, that would be of interest. In --

Q. Go ahead.

A. In the second abstract that we point to here, they speculate that the -- that it may have a long duration of action, that results from the combination of its long half-life and also the strong binding affinities that were --

that were shown in the preclinical studies.
Q. For the record, the second abstract was DTX-1283 on Page 3.
A. And they also indicate in that second abstract that the Phase II dose-ranging studies are underway, so, you know, that would suggest to a formulator POSA that, you know, that this is proceeding in the development process.
Q. Were the -- were there any Phase II results of palonosetron disclosed in the prior art that would have been relevant to a POSA?
A. There were a few reports that appeared. There was an abstract that appeared by Chelly and co-workers. This --
Q. For the record, this is DTX-0379, we're looking at Page 1.

And what year was Chelly published?
A. In 1996.
Q. Is it -- the abstracts we looked at were published in 2001. Is that unusual, for Phase I studies to be published after Phase II studies?
A. I really don't know if I know the answer to that. I mean, I think it's not unusual for studies not to be published chronologically. I mean, it really depends upon, you know, what the authors are doing and what they're involved in at the particular time.
Q. Okay. And what is disclosed here in Chelly 1996?

A. So, in this manuscript, they looked at a -- or in this abstract they report looking at a range of doses, and that would be of particular importance to a formulator POSA because it would give them some idea of the range of doses that people believed might be relevant for palonosetron, and they also indicated that there was a minimally effective dose that was found to be safe and effective. In this particular study, they were looking at postoperative nausea and vomiting. But in terms of what a formulator is going to get out of this is they're going to -- they're going to see this range of doses, and that may be a useful starting point for them in terms of designing the formulation.

THE COURT: I'm not sure the focus of this as Phase II studies. Were the IND Phase II studies directed toward PONV and CINV, counsel?

MR. WONG: My recollection is the IND was directed specifically towards CINV in this case.

THE COURT: Which is why I'm not sure what this article, Chelly, has to do with Phase II studies under the FDA IND. The Chelly article is whatever it is.

MR. WONG: Exactly.

THE COURT: But I'm not sure that it correlates to the IND Phase II studies that were going on with palonosetron.

MR. WONG: We're just reviewing all the prior art that was available on palonosetron that POSA --

THE COURT: Right, but your heading on your slide says Phase II studies.

MR. WONG: These were -- and Dr. Kirsch can testify to this, but I believe these were Phase II studies for PONV, perhaps to support a different IND, but they were published in the prior art.

THE COURT: Okay.

BY MR. WONG:

Q. Was there any other Phase II study in the prior art that disclosed palonosetron being administered to humans?

A. Yes. In addition to the Chelly abstract, there was also a manuscript that was published by Tang and colleagues, again, for a PONV, but with a similar range of doses that they looked at, 0.1 to 30 micrograms per kilogram doses, and they administered -- in this study, they administered it to the patients by intravenous administration with a volume of a 15-milliliter. So this is going to start to give the formulator some idea, not only of the dose range, but also of the concentration ranges that were -- that were deemed to be useful, at least in these Phase II studies.

THE COURT: Is that -- they're using palonosetron hydrochloride?

THE WITNESS: That's correct. That is the compound that we looked at. When we looked at the structure, we saw that, that that chloride, that's the -- that's the form.

THE COURT: It's described as isotonic sodium chloride solution.

THE WITNESS: Right.

THE COURT: That's the solution. That's not the molecule form of palonosetron.

THE WITNESS: That's correct. That's correct. They dissolved this compound, this hydrochloride salt, in sodium chloride.

THE COURT: Okay.

THE WITNESS: Isotonic sodium chloride, and then administered it.

THE COURT: Okay.

MR. WONG: And, for the record, we're looking at DTX-0276 at Pages 2 and 5.

And if I wasn't clear before, the Chelly reference we were looking at was DTX-0379.

BY MR. WONG:

Q. Dr. Kirsch, was there anything else in the prior art that would have been relevant to a POSA formulating palonosetron?

A. Well, I think the POSA would also be interested in the press releases which described the progress of palonosetron's development.

Q. Okay. Let's take a look at the first excerpt we have. It's DTX-1227 dated September 14th, 2000.

Dr. Kirsch, what does this press release disclose?

A. Well, in this press release, they point to the expected utility of palonosetron as an antiemetic for use in CINV.
Q. What about the next excerpt that's from DTX-1022 dated January 16th, 2002, what would be relevant here for a POSA developing -- developing a palonosetron formulation?
A. Well, in this one, they're reporting on some of the results of the Phase I trial, so some of the same information that we saw in the abstracts was also presented and would also be of interest to a POSA formulator.
Q. And what about the last excerpt, again, that's from DTX-1227, what is reported here in this abstract -- excerpt?
A. So here they're describing sort of the state of the -- of the development program, and they indicated that they have successfully developed the finished dosage form. So, again, this would point to the likelihood of success, I guess.
Q. Okay.
THE COURT: When they say likely -- in that September 14, 2000 excerpt, it says, "The development of the I.V. finished dosage form has been successfully accomplished," right?
THE WITNESS: Yes, that's what they state there, Your Honor.
THE COURT: And does that tell -- what does that mean to you or to a POSA? That the dosage has been selected, dosage range has been selected, or that all of the bells and

whistles of a formulation have also been finalized?

THE WITNESS: Yeah. To me, it indicates that they have decided what the final product form is, so the packaging and the end formulation, the finished dosage form.

THE COURT: Including the excipients?

THE WITNESS: Yes.

BY MR. WONG:

Q. Okay. Let's go back to the timeline.

So, after reviewing all of this prior art, how would you characterize all of the prior art available to a POSA that is trying to develop the palonosetron formulation?

A. So, I think they have a substantial amount of information about the chemistry of the compound, some of the potential technical problems that they may encounter and some ways that they may be able to overcome them. They have a pretty good idea of what the compound is going to be useful for and routes of administration and modes of administration.

Q. Okay. So let's take a look at the claims now. This here is again Kirsch 21. It's representative Claim 7. And so let's go through all of the claim limitations.

But, first, what is your understanding as to the real dispute between you and Helsinn's experts regarding the claim limitations?

A. Well, as I understand it, there are two of these elements that are being disputed, and those are the Element 4 relating

to the concentration of palonosetron, and Item 5 relating to the concentration and use of EDTA.

Q. Okay. Why don't we save those for last. Let's go through the rest of the limitations first.

Let's start with the first three, 1, 2 and 3. Was formulating palonosetron as a single-use unit-dose formulation disclosed in the prior art?

A. Absolutely. It was certainly suggested in the compound patent, but then there were a number of clinical trials that were conducted with single-use unit-dose formulations, so that was well described in the literature.

Q. What about the limitation that the formulation is an intravenous formulation? Was formulating palonosetron as an intravenous formulation disclosed in the prior art?

A. Again, it was suggested in the original compound patent and then shown to -- and then acted on, it was used as an intravenous formulation, in the -- in both in their preclinical and in the early clinical studies.

Q. Okay. I'll put a check mark there.

What about palonosetron, the use of palonosetron for reducing CINV, was that disclosed in the prior art?

A. Again, it was just at the start of the -- of the patents, the '333 patent, and then proceeding through, you know, including in the press releases, there was all indications for its potential utility in CINV.

Q. Okay. I'll put a check mark there.

THE COURT: It might also have been okay for PONV, but we're focusing on the claims of this patent at this point, right?

THE WITNESS: That's correct, Your Honor.

THE COURT: Okay.

BY MR. WONG:

Q. We're going to skip 4 and 5 for now.

Let's go to Number 6. What about the use of mannitol, was that described in the prior art as a tonicifying agent?

A. Yes. I think we saw in the Broadhead reference, for example, the recommendation to use mannitol, but there are many other references to the use of mannitol as a tonicifying agent.

Q. And what about the concentration that is described here, the 41.5 milligrams? How would a POSA arrive at that concentration?

A. So, again, I think we talked a little bit about this. I mean, you know, basically, you add the amount of mannitol that you need to bring the solution osmolarity up to the right, the proper range, so this is a fairly simple procedure.

Q. Okay. I'll put a check there.

We're at Number 7. It says 20 millimolars of citrate buffer. Was citrate buffer with palonosetron disclosed in the prior art?

A. Again, citrate buffer is one of the common buffers that is used with injectable drug products.
Q. Okay. And what about the concentration 20 millimolar, was that also taught in the prior art?
A. Yeah, that's well within the range of recommended buffer concentrations, described in Broadhead and in other references.
Q. Okay. I'll put a check mark there.

We're at Number 8. What about the limitation that the formulation has a pH of 5 or about there? Was that taught or disclosed in the prior art?
A. So, that pH is within the range that is typical for injectable drug products, and, you know, there would also be an effort using the standard development techniques to determine the optimal pH value for stability purposes.
Q. Okay. I'll put a check there.

We're at Number 9. What about the stability limitation? Would a POSA have a reasonable expectation of success developing an optimized formulation with this shelf life?
A. I believe the answer is "yes," that in the course of conducting the pre-formulation -- the formulation design and optimization studies, that they would have determined what the optimum formulation is, and that in the course of those studies, they would have determined that it was very likely to

obtain 24 months at room temperature.

I think it's also worth pointing out that, you know, another activity that the formulator gets involved in is the clinical -- the clinical trial supply, so they're involved in generating batches of drug and that, you know, these batches are -- in addition to being used in clinical trials, are also used in developmental stability studies, so that's another piece of information that they're obtaining.

Q. And would it be hard for a POSA to confirm the actual stability of any formulation, including the claim formulation?

A. Again, there is standard protocols, and this would be simply a matter of following the stability over a particular period of time with a particular storage condition. Been routine.

Q. Okay. Let's go back up. Let's start with Number 5.

Would it be obvious to use EDTA with palonosetron in a formulation?

A. So, again, the use of EDTA really hinges on the POSA's understanding of the oxidative liability of this compound, the potential for oxidative degradation, and the POSA would -- we've already -- I mean, we'll look at it again, but among the knowledge that the POSA would bring to it and that the POSA would look into is, you know, standard references on, you know, what sort of compounds oxidize.

We have here an excerpt from a well-known organic

chemistry book that describes amine oxidation and suggests that contact with air is enough to cause oxidation of amines. It also points to the appearance of amine oxides. These are N-oxides associated with tertiary amines, so the POSA would have some prior knowledge that -- that the quinuclidine ring, a tertiary amine of that sort, might undergo oxidation.

Q. Okay. And for the record, we're looking at Wade 1995, that's DTX-0344 at Page 36.

So what did the prior art teach about standard remedies for addressing oxidative degradation?

A. Well, again, there is -- there -- and we've seen this before, that the use of EDTA, for example, is a very common remedy that's used in preventing oxidation. It was mentioned in Won and also in various textbooks which also, you know, provides some reasonable concentration ranges for the use, for instance, for disodium EDTA, you know, this is the most common one that's listed in this table of chelating agents, and injectable formulations and parenteral formulations, and it gives a suitable concentration range of about .01 to .1 percent. So, you know, there's ample evidence in the literature of what the suitable range would be.

Q. And for the record, does the claimed 0.5 milligram-per-milliliter concentration of EDTA fall within that suitable range?

A. Right. So the -- the range or the concentration given in

the patent is .05 percent, so it falls right within this range.

MR. WONG: For the record, the top excerpt is Won 1995, DTX-0235, at 6. And the Swarbrick 2000 reference is DTX- -- I'm sorry, I got that mixed up.

Won 1995 is DTX-0345 at 9, and Swarbrick excerpt is DTX-0235 at Pages 6 and 8.

BY MR. WONG:

Q. So, what can we say about the limitation of 0.5 milligrams of EDTA in the claim formulation?

A. Well, I think that there was ample evidence in the prior literature to suggest the use of -- to suggest oxidative degradation, to suggest the use of EDTA, and I think that the formulator would -- would, by the methods that were standard at the time, investigate the degradation processes, confirm the oxidative instability of palonosetron, and would arrive at both the use of EDTA and the concentration.

Q. Let's look at the last limitation or the last limitation we're dealing with, Number 4.

And, first, why do you have, I guess, two values here, 0.05 milligrams per mL or 0.25 milligrams in 5 milliliters? What does that represent?

A. So, in the -- you know, we've tried to make one claim represent all of the claims in the four patents, and in the -- in the three prior patents, the concentration is what is given

for palonosetron at 0.05 milligram per mL. In the '219 patent, this same concentration is expressed as an amount in a volume, which is the same concentration.

Q. Okay. So did the prior art teach formulating --

THE COURT: Actually, the dosage of .25 milligrams is a dosage. You could put, for example, .75 as your dosage, and if you increased your volume, you could still get to the .05 concentration, right?

THE WITNESS: That's correct, Your Honor. You could also administer, you know, a tenth of a milligram and use this package and just use two mLs of it, so there is some flexibility in terms of the dosages that you could use with this particular -- with this particular structure of the product.

THE COURT: With this concentration --

THE WITNESS: That's correct.

THE COURT: -- of .05 concentration?

THE WITNESS: That's correct.

THE COURT: But when you get down to .25 milligrams, now you're specifying the dosage, correct?

THE WITNESS: Well, in my view --

THE COURT: I'm just trying to understand.

THE WITNESS: Yeah, I understand. And in my view, you could give a dosage with -- if you had .25 milligrams and 5 mL, you could give a dosage of .05 milligrams by

administering 1 mL. You could give a dosage of .1 milligram by administering 2 mLs.

You could give a dosage of .15 milligrams by administering 3 mLs and so forth, up to .25. If you needed a dosage above .25, you could use a second vial and would draw additional solution out of that.

So, you know from a formulator's point of view, I mean, the -- in my view, the critical issue is what's the concentration because what they're trying to do is to optimize the stability.

BY MR. WONG:

Q. So, does the 0.05 milligram concentration -- is that suitable for a variety of doses to be administered?

A. Yes.

Q. Okay. Did the prior art teach formulating palonosetron at low concentrations?

A. So, you know, again, what was contained in Won suggested the role of concentration -- that concentration may play a role in the stability of a palonosetron, and, you know, this would be an indication to the formulator POSA to look at concentration as a variable in stabilizing the compound, and -- and so what the POSA would be interested in doing is determining, you know, essentially what are the ranges of concentration that I might want to look at in order to find the optimal concentration. That would be sort of the starting

point for the POSA, is, you know, what range of concentrations do I want to look at. And there, there was information in the prior art that would help direct the formulator to a particular range of concentration.

Q. Okay. You mentioned the Won teaching on concentration. With respect to whether it's high or low, what did Won teach as far as concentration effects and stability?

A. Well, the Won report indicated that low concentrations, in particular, were appropriate.

Q. Okay. So let's go to --

THE COURT: And is this a low concentration?

THE WITNESS: Yes.

BY MR. WONG:

Q. So let's go to some of the prior art that were relevant to determining concentrations.

Was the Eglen 1995 disclosure, would that be helpful for -- would that be helpful to a POSA?

A. Yes. Again, what the POSA is going to do initially is to try to figure out what range of concentrations they have to operate in. You know, if they understand that concentration may be an important player in the stability of the drug molecule, then they want know, well, you know, what are my -- what are my boundary conditions in terms of investigating concentration.

And they could glean, they could obtain from a

pharmacology study, for example, some indication of what the potency of the compound of interest was relative to some other compounds, where the dose is known. And so that would provide them with some way to sort of find the bracket of concentration that they should investigate for palonosetron.

Q. Okay. So let's walk through the calculation that a POSA would do. Have you provided some calculations for the Court?

A. Right, some example calculations.

So, again, this is based on the Eglen study. What we're interesting in doing is determining sort of what the target concentration range is for the POSA to operate within to find an optimal stability. And what they would start with would be the relative potency, for instance, compared to ondansetron. And ondansetron dose was 32 milligrams -- or 32-milligram dose. From Eglen, they indicate that the potency of palonosetron was 55 times greater. So that predicts for them what a dose might be for palonosetron, for example, 0.6 milligrams.

So, now what they might want to do is to say, okay, well, you know, we have an idea, at least a rough idea, of where the dose might fall. What sort of concentration ranges would that -- would that suggest for use in a small volume parenteral? So the range of concentrations they would look at for a small volume parenteral, for instance, might range from 1 to 100 mLs, which, you know, is the compendial upper limit

for -- for concentration. So they would use that volume and that amount to determine a range of concentrations.

And so a target concentration, again, to begin the investigation of palonosetron stability might look something like .006 to 0.6 milligrams per mL. Again, that's sort of a target range, and then -- and then the formulator is going to bracket that range, probably going to go outside that range to actually begin their studies.

Q. Does this predicted target, palonosetron concentration range, is that relatively a low concentration?

A. Yes, that's a relatively low concentration.

Q. What about the -- the relative potencies of granisetron disclosed in Eglen 1995?

A. So, it would be, you know, prudent for them to not just base their calculation on ondansetron. They would likely also use granisetron, where the effective dose is 0.7 milligrams and the relative potency increase associated with palonosetron, according to the pharmacology studies, was threefold, so they get a predicted dose of 0.2 milligrams, using the concentration range that's attributed to small volume parenterals, then they get a concentration range, which is, you know, quite similar actually to the one that they calculate for ondansetron of 0.002 to 0.2 milligrams per mL.

THE COURT: Does that math work? I can't do it in my head.

THE WITNESS: Right. We're dividing 0.2 milligrams by 100 mLs to get this number here, so this is just --

THE COURT: Oh, you're dividing.

THE WITNESS: Dividing, right. And we're taking this number and dividing it by 1 mL to get this concentration here.

MR. WONG: Thank you.

BY MR. WONG:

Q. Is there any other prior art that would have been helpful to a POSA with respect to bracketing the concentration range of palonosetron?

A. Well, I think the Phase II studies might also be useful, and we're looking here at the Tang study, you know, which gave a range of doses. And so, you know, this -- a POSA might anticipate would be a range of doses that -- that may be useful, and, again, that needs to be determined by the clinician, but it gives them an idea of a range of doses and also informs them about a volume that was used, at least in this -- in this clinical trial. So they could also use this information.

So that range of doses, if we take the dose range in Tang which was, you know, very similar to the dose range in Chelly, and we -- and we calculate a dose for a 70-kilogram patient, remembering that the doses were given in micrograms per kilogram of patient weight, so if we take a typical patient at 70 kilograms, then we end up with an amount, 0.007

to 2 milligrams, and that's sort of the range of doses for a typical patient.

The volume that they used in that clinical trial was 15 mLs, so we divide these numbers by 15 mLs, and that gives us a target concentration range of 0.05 to 0.14 milligram per mL. Again, another piece of information to inform a POSA as to what concentration range they need to look at.

Q. And, for the record, the disclosures in Tang we're looking at were on DTX-0276, Pages 2 and 5.

Okay. So, Dr. Kirsch, what is here on the next slide?

A. So this is just a summary of the calculations that we made, basically, the target concentration ranges that the formulator may glean from the -- from the Phase II and pharmacology studies, and this just identifies the source of the information that they're using, and basically describes a range of concentrations, where they would begin their studies to look at how concentration might affect stability. And you can see that, really, using all three data points, the ranges are really quite similar.

So, you know, they might very well look at a range of 1 milligram per mL down to something quite low, like .001 milligram per mL in terms of looking at concentration ranges.

Q. Okay. So how would a POSA arrive at the claimed palonosetron concentration of 0.05 milligrams per mL?

A. So, from a stability standpoint, they would attempt to

optimize the concentration that provided them the appropriate level of stability, the optimized level of stability. So they would use their -- their formulation design and their formulation optimization studies to arrive at the appropriate concentration.

Q. Okay. I'll put a check mark there.

MR. O'MALLEY: Objection, Your Honor. This differs -- can you find me the slide? Where's the one where the -- I'll just object as to foundation. It's misleading. All we've heard about with respect to Number 4 is .05 mg per ml, nothing about the .25 mg, and now this check mark has shown up as to both.

THE COURT: All right. Understood.

You want to cover that, Mr. Wong?

MR. WONG: Sure.

BY MR. WONG:

Q. Does a formulator investigate the dose of palonosetron? Would a formulator be in charge of doing those kind of studies?

A. No. That -- deciding on the dose is the -- is the task of the clinician.

Q. Okay. And so how would the formulator work with the clinician in arriving at the final concentration that is going to be used in the optimized product?

A. They would, you know, take this dose and devise a

configuration, in this case, a volume that would be consistent with the optimum concentration.

Q. Okay. So --

THE COURT: You can cover it on cross. I understand the caveat with the Line 4 there.

BY MR. WONG:

Q. So let's look at the entire claim, Claim 7. If a POSA were developing a palonosetron formulation as of January, 2003, would a POSA have been motivated to combine the claim elements listed here and have a reasonable expectation of success in achieving this formulation?

A. Yes. I believe that, you know, with the information that was available in the prior art and the methodologies, the routine methodologies that they use, that they would.

Q. And would a POSA also have a reasonable expectation of success that the formulized -- that the formulation would have an optimized stability of 24 months when stored at room temperature?

A. Yes.

THE COURT: Is that a pretty typical stability standard that a formulator wants to aim for in developing an intravenous small volume product?

THE WITNESS: I think that it's typical, but it's not a requirement, by any means. You know, there could be other storage conditions and other time periods, and a product could

still be useful in -- for human use.

THE COURT: So stability is, to some degree, a function of what your active ingredient is and how stable you can get it to be?

THE WITNESS: That's right.

THE COURT: Right?

THE WITNESS: It is in some respects an inherent property, yes.

THE COURT: Um-hum.

MR. WONG: Thank you, Your Honor.

BY MR. WONG:

Q. Let's go back to the product development slide.

So let's cover one issue here. What is your opinion of plaintiffs' requirement that a POSA would need to select palonosetron among other drug candidates in the first place?

A. Well, in my opinion, the POSA here is a formulator, and the formulator is provided with a product profile and the active ingredient included in that product profile, so the starting point of what the formulator does is, you know, listed here as the product profile point, and that, you know, decisions about what active ingredient to be -- to be used are not what the formulator does.

Q. Okay.

THE COURT: How about the dosage? Does that come at the point where the formulator gets the assignment? Or at

least the dosage range?

THE WITNESS: There may be some notion of what the dose range is based on preclinical studies. I think, you know, it is the -- it's the Phase II studies where the dose is actually determined by the clinician, so that information may come later.

THE COURT: But it feeds into the formulator's work?

THE WITNESS: Yeah, absolutely. You know, they're working as a project team. They're collaborating in this entire process.

BY MR. WONG:

Q. Assuming that the selection of palonosetron is relevant, would a POSA have been -- would a POSA, in fact, have been motivated to develop a palonosetron I.V. formulation?

A. In my reading of the -- the prior art, the history, you know, there was ample suggestion that palonosetron could be effectively used as an antiemetic. So, in my estimation, there is, you know, adequate evidence in the clinical trial results that were reported, in the -- in the press releases that were reported, in the preclinical studies which suggested its use, so, in my estimation, there was adequate information to pursue this.

Q. Okay. Let's wrap up.

Let's -- do you have opinions on plaintiffs' alleged secondary considerations in this case?

A. Yes, I do.
Q. Okay. So what is your opinion as to whether or not treating delayed emesis was an unexpected result?
MR. O'MALLEY: Objection, Your Honor. It's beyond what he's been qualified for as an expert in this case.
THE COURT: Is it in his expert report or not?
MR. WONG: It is.
THE COURT: Okay. But I understand that we had in limine issues that I would take up at trial.
MR. O'MALLEY: Yeah. I'll just pose my objection.
THE COURT: Umm --
MR. WONG: I can rephrase the question.
THE COURT: All right.
BY MR. WONG:
Q. With respect to the formulation of -- the claimed formulation of palonosetron, what is your opinion as to whether the claimed formulation provided an unexpected result in terms of delayed emesis?
A. Right. So, it's my opinion that the formulation is not a contributing factor to the pharmacological or therapeutic effectiveness of palonosetron, that the formulation is there for stability, for maintaining a stable product, and that the excipients and ingredients there are not -- are not a contribution to its -- its effectiveness.
Q. From a formulation perspective, do you have any

understanding of whether the inactive excipients in the claimed formulation have any role in the efficacy of the API palonosetron?

A. I would not anticipate that any of them play any role in how palonosetron acts when it's injected into the -- into the vein.

Q. What about -- so I'll put a "no" there.

What about the second bullet point? What is your opinion as to whether or not the claim formulation has an unexpected pharmaceutical stability?

A. I don't believe that that was unexpected result at all. I mean, that was the whole purpose of the development process and that there was not an unexpected result.

Q. And what about the last bullet points, what are your opinions as to whether the claim formulation of Aloxi®, embodied in Aloxi®, was necessary to obtain regulatory approval?

THE COURT: Is that a factor? I thought this nexus between the FDA-approved product and public acceptance of the products -- popularity of the product in the marketplace, not nexus between putting an application in and getting FDA approval.

MR. WONG: That was our point, too, but we've seen that in expert reports, and we just wanted Dr. Kirsch to address it.

THE COURT: Let's pass that one by.

MR. WONG: Okay. That's fine.

THE COURT: Do you agree, Mr. O'Malley, that we pass that one by?

MR. O'MALLEY: It's misstated something. I don't know what that relates to in our proofs.

MR. WONG: If it comes up on -- in their case in chief, we can address it on cross.

THE COURT: Okay.

MR. WONG: Thank you. No further questions.

THE WITNESS: Thank you.

THE COURT: All right. Fine. Would you like the lunch recess or would you like to do the cross?

MR. O'MALLEY: Probably makes sense to do the lunch recess and --

THE COURT: I think so.

MR. O'MALLEY: -- start this after lunch.

THE COURT: Okay, good. Thanks. As soon as you're ready, we'll resume.

MR. O'MALLEY: 1:00?

THE COURT: That's fine.

(Luncheon recess taken.)

THE COURT: Okay. Let's proceed.

MR. O'MALLEY: May I approach the witness, your Honor?

THE COURT: Sure.

MR. O'MALLEY: I put a set of these exhibits on your shelf over there.

THE COURT: Okay.

CROSS-EXAMINATION BY MR. O'MALLEY:

Q. And Dr. Kirsch, these exhibits, as has been occurring throughout trial, will be on your screen or in the book, whichever is more convenient for you to refer to.

A. Okay.

Q. Dr. Kirsch, you're not a marketing specialist in pharmaceuticals, correct?

A. That's correct.

Q. And you haven't been trained to assess what market attributes cause clinicians to prescribe one medicine versus another, correct?

A. That's correct.

Q. Now, you're not an expert in pharmacology, correct?

A. That's correct.

Q. And you're not an expert with respect to selecting compounds for development, correct?

A. That's correct.

Q. You haven't ever designed a clinical trial to determine the efficacy of a drug product, have you?

A. No, I have not.

Q. And you're not an expert in antiemetics, correct?

A. That's correct.
Q. You may need to get closer to the mic. I'm having trouble hearing you.
You haven't made any study of the clinical pharmacology of antiemetics, is that correct, outside of this litigation?
A. That's correct.
Q. You're not an expert in treating nausea and vomiting, correct?
A. That's correct.
Q. And you aren't, therefore, opining or offering any opinions on what would cause a physician to prescribe Aloxi® over some other antiemetic drug, correct?
A. That's correct.
Q. You're not an expert in clinical studies, correct?
A. That's correct.
Q. And you're not an expert in clinical sciences, correct?
A. That's correct.
Q. Now, you started your work at Lilly in 1982; is that correct?
A. That is correct.
Q. And you worked at Lilly for over 10 years?
A. That's correct.
Q. As I understand, you left Lilly in November of 1994?
A. That's correct.
Q. Now, you worked on the formulation teams for 20-some-odd

projects as I understood your testimony; is that correct?
A. That's correct.
Q. And only six received FDA approval out of that 20 or so projects, correct?
A. That was an estimate, yes.
Q. And for the rest of the projects you worked on, you've testified that whatever caused them to not receive approval, it had nothing to do with the formulation, correct?
A. That's correct.
Q. So, some of those projects presumably did not receive approval because they failed due to safety and efficacy concerns?
A. That's my recollection, yes.
Q. Okay. Would that be all of the 14 or so that did not receive FDA approval?
A. Um, to the best of my recollection, that's correct, yes.
Q. Okay. Did some of those 14 that didn't receive FDA approval fail in Phase III?
THE COURT: If you recall.
BY MR. O'MALLEY:
Q. If you recall.
A. I don't recall. I don't recall if it was Phase II or Phase III.
Q. All right. Now, you were a group leader at Lilly from 1987 to 1994. Did I understand that right?

A. I think I became a group leader in '84.
Q. And that's the position you held until you left Lilly?
A. Well, that was my -- that was my functional position. My title changed over the course of --
Q. Okay. Now, you never selected a particular active ingredient for formulation development while you were at Lilly, correct?
A. That's correct.
Q. And in connection with the formulation projects you worked on while at Lilly, you never selected the active ingredient dosage amount, did you?
A. No.
Q. "No" you agree with me?
A. I do agree with you.
Q. Okay. In fact, it was members of the clinical portion of the team that selected the dosage amounts when you worked on drug development projects at Lilly, correct?
A. That is correct.
Q. Now, you do consulting work, correct?
A. I'm sorry.
Q. You do consulting work, correct?
A. I do some, yes.
Q. Okay. You haven't ever selected a particular active ingredient for formulation development as part of your consulting work, correct?

A. That's correct.
Q. And you haven't ever advised an organization developing drug products regarding what clinical dose to use in a formulation; is that correct?
A. Yes, that's correct.
Q. Now, I'd like to talk about the universe of materials you considered in forming your opinions in this case.
First of all, you haven't consulted with any other experts in this case, correct?
A. That is correct.
Q. And you haven't reviewed any reports submitted by any expert testing on behalf of any other defendant in this litigation, correct?
THE COURT: Is that question clear to you?
THE WITNESS: Your question is what expert reports I have seen?
BY MR. O'MALLEY:
Q. Yeah, let me state it again and see if I can make it clear.
A. Okay.
Q. You haven't reviewed any reports submitted by any expert testifying on behalf of any defendant in this litigation, correct?
A. No, I don't believe that's correct.
MR. O'MALLEY: Let me look at Kirsch Deposition

Transcript 19, Lines 18 to 22. Eric, do we have that? And this would be the April 30, 2014 deposition transcript.

If I may approach?

THE COURT: I don't need it. I'll look at it on the screen.

MR. O'MALLEY: Okay.

THE COURT: Okay. Thanks.

BY MR. O'MALLEY:

Q. "QUESTION: Did you review any reports submitted by any expert testifying on behalf of any defendant in this litigation?

"ANSWER: No."

Did I read that correctly?

A. You read that correctly.

Q. Well, let's be a little more specific in case that was just a mistake.

You haven't reviewed the expert reports of Dr. Reddy's formulation expert Dr. DeLuca, correct?

A. No, I don't believe I have seen Dr. DeLuca's report.

Q. Okay. And you haven't reviewed the expert reports of Reddy's formulation expert, Dr. DeLuca, correct?

MR. WONG: Objection. I think it was asked and answered.

THE COURT: I think that's the same question.

MR. O'MALLEY: You are absolutely right. Withdrawn.

THE COURT: Deposition transcript maybe?

MR. O'MALLEY: Yes, that's what I intended.

BY MR. O'MALLEY:

Q. You haven't reviewed the deposition testimony of Dr. DeLuca either, have you?

A. I don't recall seeing it, no.

Q. Okay. So, that's fair to say you haven't taken any analysis of the extent to which, if any, Dr. DeLuca's opinions conflict with your own?

A. I have not conducted that analysis, no.

Q. Okay. Now, at your most recent deposition in this case, do you recall going through the various references that were listed on the face of the '219 patent with my associate and comparing them to the references you rely on for your obviousness opinion?

A. I do recollect having that discussion with him, yes.

Q. And do you recall him pointing out to you that each of the references you rely on are cited references on the face of the '219 patent?

A. I do recall that, yes.

Q. Okay. Now, I would like to look at the '219 patent, DTX-0248, Page 6.

MR. O'MALLEY: In the right-hand column, if you can find that for me, Roy. There we go.

BY MR. O'MALLEY:

Q. Do you see that your own expert report in this litigation is among the references cited on the face of the '219 patent?
A. Yes, I do see that.
Q. And do you understand, from the date, that that was the first expert report that you submitted in this litigation?
A. I believe that's correct.
Q. Okay.
THE COURT: There may have been a claim construction report separate from that expert report, but I'll allow you to question him.
BY MR. O'MALLEY:
Q. That report, if you need to verify my question, should be in your notebook.
A. Again, DTX-0268?
Q. Yes. So, if you'd turn to DTX-1175.
Do you see that?
A. Yes, I do see it.
Q. And let's turn to the back page for the date. There's an appendix, actually. There we go.
Do you see that's dated September 9?
A. Yes. I see it's dated that.
Q. Okay. And do you see that that's your first expert report you submitted in this litigation?
A. That is my recollection, yes.
Q. Well, you can look at the table of contents if that helps

you.

Do you see that?

A. Uh-huh.

Q. And do you see that this is the report whereby you summarize your opinions as to obviousness at least as to the first three patents-in-suit?

A. Yes, that's correct.

Q. Now, your opinions as to obviousness, do you have any difference in the structure of your opinions with respect to the '219 patent versus the first three patents-in-suit?

A. In general, I don't believe so.

Q. Okay. So, now going back to '219 references cited just to close the loop, Page 6, and there it is there.

Do you see, again, this expert report containing your opinions of obviousness, at least with respect to the first three patents-in-suit, is one of the references cited on the face of the '219 patent.

Do you see that?

A. Yes, sir, I do.

Q. Okay. Now, you've testified that you were first retained in connection with this action roughly towards the end of 2012 or maybe early 2013.

Do you recall that?

A. I believe that those dates are correct, yes.

Q. Okay. Now, let's look at Teva's invalidity contentions.

And I don't have a DTX number. They're in your notebook while we pull them up.

Oh, okay. Have you located those, or do you want to look at them from the screen?

A. The screen, I think, will be okay.

Q. Have you seen these before?

A. Yes, I believe I have.

Q. Okay. Now, let's look at Page 47.

Do you see the date for these contentions, December 1, 2011?

A. Yes.

Q. Yeah, and that's about a year before you were retained by Teva, correct? As best you recall?

A. As best as I recall, that's correct.

Q. Okay. Now, let's take a look at Page 4 of Teva's invalidity contentions.

Do you see there's a heading on Page 4 with the title "Identification of Prior Art Under L.Pat.R.3.3(a)"?

A. Yes, I see that title.

Q. And if you turn to Page 5, you see a list of references, correct?

Do you see that?

A. Yes, I do.

Q. And do you see the first reference is what the parties have been referred referring to, Eglen, 1995.

Do you see that?
A. Yes.
Q. And that's one of the references you relied on today as part of your obviousness analysis?
A. It is.
Q. Now, you testified that you did a prior art search; is that correct?
A. That's correct.
Q. Well, let's continue. Now, the next reference is what the parties have been referring to as Tang, 1998.
Do you see that?
A. I do.
Q. And, again, that's one of the references you relied on for your testimony today?
A. That's correct.
Q. Now, the next reference is the '333 patent.
Do you see that?
A. Yes, I do.
Q. And, again, that's one of the references you relied on today?
A. It is.
Q. And the next reference after that is Wade.
Do you see that?
A. I do.
Q. And, again, that's one of the references you relied on

today, correct?
A. That's correct.
Q. And if you move down to No. 7, we see Won.
Do you see that?
A. I do.
Q. And that's one of the references you relied on today?
A. That's correct.
Q. Now, if we turn to Page 6 of Teva's invalidity contentions and look at reference number 8, that's the Clark, 1993 reference.
Do you see that?
A. It is.
Q. And that's one of the references you relied on today, correct?
A. That's correct.
Q. And if you move down to reference 10, that's the Broadhead reference.
Do you see that?
A. I do.
Q. And that's one of the references you relied on today?
A. That's correct.
Q. If you move down to reference Number 19, that's the Wells, 1998 reference, correct?
A. That's correct.
Q. And that's one of the references you've relied on today?

A. Correct.
Q. And if you move down to reference 20, that's the Swarbrick reference.
Do you see that?
A. I do.
Q. And that's one of the references that you've relied on today?
A. That's correct.
Q. Now, I would like to turn to your definition of POSA.
A. Okay.
Q. Now, your definition of POSA is, basically, a pharmaceutical formulator, correct?
A. That's correct.
Q. So, your POSA definition does not include clinicians, correct?
A. That's correct.
Q. Or pharmaceutically trained marketing people, right?
A. That's correct.
Q. Or pharmacologists, correct?
A. That's correct.
Q. The -- Well, do you recall testifying at trial in the AstraZenica v. Anchen, A-N-C-H-E-N, case in front of Judge Pisano?
A. Yes, I do.
Q. Let's look at Page 5 of Judge Pisano's AstraZenica

opinion, and I just want to highlight Claim 1.

And, basically, it was a formulation claim including a sustained-release formulation of a gelling agent, a certain active ingredient defined there, and a pharmaceutically acceptable salt together with one or more pharmaceutically acceptable excipients.

Do you recall that?

A. Yes, I recall it.

Q. And that's what you referred to as a formulation claim?

A. Well, there was more specificity later on, but, yeah.

Q. Okay. And like in this case, you testified that with respect to the identity of the POSA "that the '437 patent is all about formulation and that no clinician is necessary in the POSA definition," correct? Do you recall that generally?

A. I believe that's correct, yes.

Q. Okay. And are you aware that Judge Pisano rejected your definition of a POSA and specified that a clinician was included in the definition of a POSA?

A. Um, I think generally what you're saying is correct.

Q. Okay. And I don't want you to take my word for it. Why don't we pull up Page 21 of the decision. Starting with "Consequently". And this is, I'll represent to you, the district court decision: "Consequently, upon examination of all of the evidence presented at trial, the Court finds that the person of ordinary skill in the art pertinent to the '437

patent would include a clinician or an antipsychotic drug researcher in addition to the formulation scientist as described earlier."

Do you see that?

A. Yes, I do see that.

Q. Okay. Now, I want to talk about -- a little bit about the '333 patent that you discussed, DTX-0343.

Now, I believe you cited this for motivation -- and I'm paraphrasing, so forgive me, correct me if I have this wrong -- for motivation for a POSA to pursue an I.V. formulation of palonosetron; is that correct?

A. Yes, I think that that's --

Q. Among possible other things you cited to the Court?

A. Yeah, that's a fair statement, yes.

Q. Well, you would agree that the '333 patent discloses other dosage forms other than I.V., correct?

A. It does.

Q. In fact, let's look at PTX- -- let's look at this exhibit, Column 12, Lines 25 to 35.

And it states, "In general, compounds of Formula I will be administered as pharmaceutical compositions by one of the following routes: Oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous, or subcutaneous.) Compositions can take the form of tablets, pills, capsules, semi-solids

powders, sustained-release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are considered of, in general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient."

Do you see that?

A. I do see that.

THE COURT: Counsel, you just misspoke when you said the word "considered" the word was "comprised."

MR. O'MALLEY: I'm sorry. Thank you.

THE COURT: That's okay.

MR. O'MALLEY: Thank you, your Honor.

THE COURT: You're welcome. You don't have to go back.

BY MR. O'MALLEY:

Q. Now, when you were discussing the '333 patent --

MR. O'MALLEY: And just give me a moment, can we put up Kirsch Demo 13?

BY MR. O'MALLEY:

Q. You were -- you provided some testimony on this structure shown blown up in Kirsch Demo 33.

Do you recall that?

A. Yes, I do.

Q. And you describe what a POSA -- some of the opinions a POSA would form in response to looking at that chemical

structure, correct?
A. Yes.
Q. Now --
THE COURT: Counsel, for the record, you're referring to the chemical structure for palonosetron that's depicted there as RS-25259-197?
MR. O'MALLEY: Thank you, your Honor.
BY MR. O'MALLEY:
Q. Now, you realize that that structure itself as shown here never appears in the '333 patent, correct?
A. It's described in words.
Q. It's described in words. You don't see the structure, correct?
A. That's correct.
Q. Now, if we can turn to Example 13, Column 29 of the '333 patent. And let's back up to Column 28. From the bottom, continuing over to the top of Example 13, continuing through the three formulations.
Now, you've provided some testimony about the intravenous formulation disclosed in the '333, correct?
A. Yes, I did discuss that.
Q. Okay. But there's also a disclosure of an oral formulation, correct?
A. There is.
Q. And there's also a disclosure of a tablet formulation,

correct?
A. That is correct.
Q. Now, you're aware that there's no human efficacy data in the '333 patent for any of the compounds encompassed with the genus of the '333?
A. Yes, that's correct.
Q. And you understand what I mean by genus of the '333?
A. The compounds that are listed in '333.
Q. The '333 actually discloses quite a number of compounds, correct?
A. Yes, it does.
Q. Now, if you look at the intravenous formulation -- and, again, this is the only example of any intravenous formulation in the '333; is that correct?
A. Yes, that is correct.
Q. And it doesn't specifically disclose a formulation of palonosetron, correct?
A. It does not.
Q. And no efficacy data is disclosed for this formulation, correct?
A. That's correct.
Q. And no stability data is disclosed in the patent for this formulation; is that also correct?
A. Yes, that's correct.
Q. Now, within Example 13, it discloses a dosage for the

compound of the example, correct?
A. Yeah, I mean, the compounds, I guess.
Q. Compounds, right.
A. Right.
Q. It could -- this example could be very many compounds.
A. That's correct.
Q. And the dosage it discloses for those very many compounds is from 10 to 100 milligrams; is that correct?
A. The amount of the formulas in that formulation --
THE COURT: Can't hear you.
THE WITNESS: The amount of that -- of the compound in that formulation.
BY MR. O'MALLEY:
Q. Is 10 to 100 milligrams.
A. 10 to 100 milligrams.
Q. Now, at the lower limit, 10 milligrams, that's 40 times .25 milligrams. Did I do that math correct?
A. Yeah. I mean, it's much, much greater.
Q. Much greater than .25.
Now, all of the questions to you, posed to you in the morning relating to your overarching opinion related to what would be relevant to a POSA formulating palonosetron, correct?
A. That is correct.
MR. O'MALLEY: Now, I'd like to look at Kirsch Demonstrative 6, please.

BY MR. O'MALLEY:

Q. Now, you talked about the various steps that were involved in formulation development.

Do you recall that?

A. I do recall that.

Q. And one of the steps involved in that process involved a product profile, correct?

A. That's correct.

Q. Now, is your POSA involved in the product development at that stage of developing the product profile?

A. No.

Q. That would be clinicians, marketing people, whom?

A. Yes, clinicians and marketing people for the most part.

Q. Okay. Now, one of the things you stated that they do as part of that process is discuss known or likely competitors, correct?

A. Yes. That's typically part of the product profile.

Q. And I believe in response to Judge Cooper's question, you said that that would be -- that would involve discussions of similar compounds.

Do you recall that?

A. I don't recall my discussion.

Q. Well, would that involve discussions among those persons you identified, the marketing and clinicians, with respect to possible competitive products in the same therapeutic

category, for example?
A. Yeah, I think typically in the product profile, you know, there's a list of competitor products that's included in that.
Q. And it's going to include at least products in the same therapeutic category, correct?
A. Definitely in the same therapeutic --
Q. Okay.
A. -- category.
Q. All right. Now, by 2000 --
MR. O'MALLEY: You can take that down, Roy.
BY MR. O'MALLEY:
Q. By 2003 a POSA, even assuming it's a formulator, would have been able to know that Roche had stopped its own development of palonosetron and had out-licensed the product to Helsinn, correct?
A. I believe that information was publicly available, correct.
Q. And that POSA would have known through press releases and the like that Roche subsequently purchased rights to a different setron in 2000 for over a billion dollars, correct?
A. I believe that that was publicly known information. I don't know whether a POSA would have -- would have picked up on that or not.
Q. You don't believe that a POSA, your POSA, picks up on press releases relating to the progress of setrons?

A. It's conceivable. They might be focused especially on palonosetron.
Q. I'm sorry?
A. They may be focused especially on the compound that they've been assigned to develop.
Q. Palonosetron.
A. That's right.
Q. And, indeed, in your discussion of your obviousness references, you rely on several press releases, correct?
A. Yes. Press releases related to palonosetron, right.
Q. Now, let's take a look at PTX-0042. And do you see that, in part, this is relating to, and I'm going down to the second paragraph, the fact that "SmithKline is also selling rights to chemotherapy drug Kytril to Roche AG for $1.23 billion in cash."

Do you see that?
A. I do see that.
Q. And do you see that this is a Dow Jones newswire dated August 31, 2000?
A. Yes, I see that.
Q. And a POSA in this relevant time period would have recognized that Kytril was the brand name for granisetron, correct?
A. They probably would have recognized that that was the brand name for Kytril; that's correct.

Q. Now, this same press release announcing Roche's purchase had some discussion of what the analysts thought about this purchase.

Do you see that?

A. You'll have to point me to it. I've not studied this.

Q. Do you see that it starts, "Analysts agree Roche's acquisition makes a lot of sense."

Do you see that?

A. Yes, I see that.

Q. And then down later it states that "What is true in both cases is that when you buy a drug that has already been successfully marketed, there is no risk compared to big spending on research and development for new products," said that particular analysis, correct?

A. Yes, that is what it says.

Q. Now, if you have no opinion on this, that's fine, that may be out of your bailiwick, but do you agree or disagree with that analyst's opinion as to the relative risks of buying an old, established product versus establishing your own?

A. Well, it is true that there's big spending associated with research and development. I certainly agree with that.

Q. Okay. So, the fact that the POSA knows that Roche's has out-licensed palonosetron in the late '90s to Helsinn and then in 2000 purchases another setron, certainly that POSA would conclude that Roche did not out-license palonosetron because

it was getting out of the antiemetic field; is that fair?
A. I'm not sure to what extent the POSA would make that analysis.
Q. Okay. Were you in the courtroom when Dr. Calderari testified about a preface to the CMC summary volumes prepared by Dr. Thomas Malefyt, explaining why Roche terminated its palonosetron program?
A. I was in the courtroom definitely. I don't recall the discussion.
MR. O'MALLEY: Okay. Let's take a look at PTX-0263.0001.
MR. WONG: Objection, Your Honor. This is not prior art. There's no foundation for this witness.
THE COURT: I can't hear you.
MR. WONG: This reference is not prior art. It's not publicly available. There's no foundation with this witness.
MR. O'MALLEY: Well, the witness has said he wouldn't know what to conclude from the publicly available prior art. I'm just seeing if this shines any light on it. I can move on, though. It's not important. Why don't I move on.
THE COURT: That's fine.
BY MR. O'MALLEY:
Q. Now, let's take a look at PTX-0256. Now, this is a publicly available article.
Do you see that?

A. Yes, I do see that.
Q. And --
THE COURT: By an economist, right?
MR. O'MALLEY: By an economist, but it includes discussions from Roche folks, Syntex/Roche folks.
THE COURT: Okay.
BY MR. O'MALLEY:
Q. And you considered Dr. Amidon's report?
A. Yes, I did.
Q. And the exhibits to Dr. Amidon's report?
A. I did consider them.
Q. And do you recall this is one of the exhibits to Dr. Amidon's report?
A. No, I'm sorry, I don't.
Q. Okay. Do you recall reviewing this article at your April 30, 2014 deposition?
A. Not really, no.
Q. Okay. This article is dated 1997; is that correct? Probably upper right-hand corner.
Do you see that?
A. Yes, I do.
Q. And this article would have been available publicly to a POSA in January 2003, correct?
A. Yes, it would have.
Q. Now, let's turn to Page PTX-0256.0006. And in the right

side column, the second paragraph reads and begins, "Paul Freiman, former chief executive of Syntex, Palo Alto, California, has provided two case history examples of how pharmacoeconomics have helped to shape the R&D portfolio of that company (personal communication)."

Do you see that?

A. Yes, I see that.

Q. And if you turn to the next page PTX-0256.0007, it discusses the second case that was being discussed with the former chief executive of Syntex, correct?

A. Let me look at it.

Q. The paragraph begins, "The second case history," but read as much as you need.

And I'll just read that full sentence. You see it states that "The second case history involved the development of an antiemetic drug in the serotonin$_3$ (5-hydroxytryptamine$_3$);5-HT$_3$ receptor antagonist class."

Do you see that?

A. Yes, I do.

Q. Then it states, "This is a relatively new drug class with only two products on the U.S. market in the first part of the 1990s, ondansetron and granisetron."

Do you see that?

A. I see that.

Q. And it continues that "Animal data suggested that the

proposed product would have a significant incremental gain in efficacy over these existing products. However, a specific larger gain in efficacy was projected as being necessary for this product to demonstrate cost effectiveness at the price level that would be profitable on rate-of-return grounds."

Do you see that?

A. I do.

Q. Now, in this time period, late '90s, you aren't aware of any 5-HT_3 antagonist antiemetic that was being developed by Syntex in this time period other than palonosetron, correct?

A. I'm not aware of what they were in development stages with at this time.

Q. Now, the paragraph concludes, "Accordingly when the targeted gain in efficacy was not realized in Phase II studies, this product was terminated before undertaking major Phase III clinical trials."

Do you see that?

A. I do see that.

Q. So, a POSA in 2003 would be able to glean from this publication that Roche terminated its palonosetron because it did not meet Roche's efficacy goals, correct?

MR. WONG: Objection. Foundation.

THE COURT: I'll allow it if he can answer.

Would your POSA be reading this article?

THE WITNESS: Probably not. You know, this doesn't

make reference to palonosetron.
BY MR. O'MALLEY:
Q. So your POSA only --
THE COURT: It may make reference to it, but it doesn't say it.
THE WITNESS: That's correct.
THE COURT: Right?
BY MR. O'MALLEY:
Q. So let me clarify that. You don't believe the POSA would know that this is referring to palonosetron?
A. I think the POSA is focused on collecting information that would be relevant in his formulation development efforts.
Q. And, so, your POSA collects press releases related to palonosetron, correct?
A. That's correct.
Q. And your POSA would know from the fact that Roche only has one 5-HT_3 in the literature at this time that this was likely referring to palonosetron, correct, whether the word is there. We've seen Eglen, et cetera, all the things you've shown us, Piraccini.
A. Well, again, I don't know too many formulators that spend time reviewing economics journals --
Q. And how many --
A. -- but certainly they would see press releases. I get press releases across my desk all the time.

Q. But you don't think a POSA would have seen this.
A. I don't really know.
Q. Let's take a look at PTX-0254. And do you see this is a review article?
Do you see that?
A. Yes, I do.
Q. And it's discussing, the title is "Antiemetics in Development."
THE COURT: Did you say this is a review or a reviewed?
MR. O'MALLEY: A review article.
THE COURT: Okay. So, it's kind of a compendium of literature?
MR. O'MALLEY: Yes, rather than --
BY MR. O'MALLEY:
Q. Could you please explain to the Court what the term of art "review article" means?
A. Certainly.
So, review article discusses sort of the state of the art with regard to some topic and draws on knowledge and publications that have, you know, shown up prior and, you know, attempts to draw some inference and understanding of the state of the art.
Q. And do you see that the publication date is -- I think it is at the bottom of the abstract -- 2002. It should be also

at the bottom of the page there.
A. Yes, I saw that.
Q. Okay. Let's turn to Page PTX-0254.0003 at the bottom of the page under Section 5. And I want to focus first on the second sentence.
Well, let me back up to the beginning. "The role of 5-HT_3 receptor antagonists in various N and V states is well established and has been discussed. Numerous agents in this class are currently marketed worldwide, and their efficacy and safety are indistinguishable."
Do you see that?
A. I see that, yes.
THE COURT: What is N and V?
BY MR. O'MALLEY:
Q. Do you know what N and V means?
A. Nausea and vomiting.
Q. Now, would your POSA read this article?
A. Yes, I believe they would.
Q. Okay. Certainly, clinicians and marketing people developing a drug in a field of antiemetics would -- this is the type of material they would review to, as you put it, see what the known competition landscape was out there, correct?
A. I think that's correct, yes.
Q. Now, this statement with respect to the 5-HT_3s being indistinguishable in their efficacy and safety, you have no

reason to disagree that this statement was accurate as of 2002?

A. No, I have no reason to disagree with that statement.

Q. Okay. Let's turn to Page 0254.0004 under Heading 8, Expert Opinion and Conclusions. It states that "The NK-1 receptor antagonists are the most promising and vigorously studied agents in development for the managing of nausea and vomiting," and it should have been management.

Do you see that?

A. Yes, I see that.

Q. And you did not have any basis to disagree with that statement as to the state of the art as of 2000, do you?

A. I have no basis to -- to comment on it.

Q. Now, do you recall in your AstraZenica testimony you testified that "Marketing drivers would be among the things that would motivate a formulation scientist to a particular type of formulation?"

Do you recall that generally?

A. You know, I believe that there was some discussion about that.

Q. You don't recall that?

A. Not specifically.

Q. Now, in preparing your expert opinions in this case, you reviewed the expert reports of Dr. Gordon Amidon, correct?

A. I did.

THE COURT: That's one of your experts?

MR. O'MALLEY: Yes, your Honor. That's our primary formulation and obviousness expert.

His report's in your binder if you need it, but we'll put it up on the screen. Paragraph 58 of his rebuttal report, please. And, first of all, let's go to the front page before we go to this.

BY MR. O'MALLEY:

Q. This is the rebuttal expert report of Gordon Amidon.

Do you see that?

A. Yes, I do.

Q. And let's go to the date, for the record. And you see it's dated October 25th, 2013?

A. Yes.

Q. And you recall reviewing this expert report, correct?

A. Yes, I recall reviewing it.

Q. And do you recall that this report provided Dr. Amidon's rebuttal opinions to your opinions in your first expert report that we discussed earlier, September 9, I think it was.

A. Yes.

Q. Do you recall that?

A. Yes, I recall that.

Q. Now, if we can go back to Paragraph 58 of Dr. Amidon's report, he states that "By 2002, enthusiasm had actually faded for 5-HT_3 compounds as a class." And then he goes on to cite

Dr. Saab and various publications.

Do you see that?

A. Yes, I see that, uh-huh.

Q. Okay. Now, you testified at your deposition that you have no reason to disagree with Dr. Amidon's conclusion in Paragraph 58, correct?

A. I don't recall that I said that, but I agree that I don't have any reason to disagree.

Q. And turning to Paragraph 59 of Dr. Amidon's October 25, 2013, report it states at the beginning of the paragraph, "The lack of enthusiasm for 5-HT_3 compounds was compounded by the fact that multiple versions of three different 5-HT_3 compounds were available in the U.S. market alone by 2002."

Do you see that?

MR. WONG: Objection, Your Honor, to the extent counsel is just reading from one of their own expert reports.

THE COURT: I'll allow some latitude here on cross.

BY MR. O'MALLEY:

Q. Do you see that?

A. Yes.

MR. O'MALLEY: And for the record, it is a matter of convenience to read from the report. I obviously could just ask him if he disagrees with that proposition, but the words are here for me.

BY MR. O'MALLEY:

Q. And you don't disagree with that statement either, correct?
A. I don't have a reason to disagree with that statement. I don't really have an opinion about it.
Q. Okay. And then later in the paragraph, it states --
THE COURT: So you're not adopting that as part of your opinion.
THE WITNESS: That's correct.
THE COURT: Okay. Fine.
BY MR. O'MALLEY:
Q. It states, "By the filing date of the patents-in-suit in 2003, the economic prospects associated with potentially bringing another 5-HT_3 compound to the market would have grown particularly dim in light of the knowledge that ondansetron would be going generic around 2005."
You have no basis to disagree with that opinion, correct?
A. I have no basis to disagree with that opinion.
Q. Now, these are the type of factors that in your formulation development process that that first group of folks, the clinicians and the marketing folks, these are the type of factors that they would have to consider in choosing an active ingredient for development. Can we agree on that?
A. We can agree on that.
Q. Now, earlier today you testified that the Piraccini

abstracts would provide a motivation to develop palonosetron, correct?

And if I misunderstood you, please correct me.

A. Well, I think the Piraccini abstracts that were Phase I studies provided information about the pharmacokinetics of palonosetron --

Q. Okay.

A. -- which was distinct from other setrons.

Q. So, you're not offering an opinion that the Piraccini abstracts would provide a motivation to develop palonosetron in the 2003 period, as opposed to other antiemetics; is that fair?

A. Well, there's certain aspects in the Piraccini abstracts that would be useful to a palonosetron (sic) developing I.V. formulations.

Q. Would be useful to a POSA who was already assigned to develop a formulation of palonosetron?

A. Yes, that's correct.

Q. Okay. That's --

THE COURT: Hold on just a minute.

When you said there's certain -- Doctor, when you said that there's certain aspects in the Piraccini abstracts that would be useful to, you said to a "palonosetron" instead of to a POSA.

THE WITNESS: I'm sorry. Did I say that? I

apologize.

THE COURT: You meant POSA, right?

THE WITNESS: Yeah, I did mean POSA. Thank you.

THE COURT: Okay.

BY MR. O'MALLEY:

Q. So you would believe they would be useful to this POSA who's already assigned the project of developing a palonosetron formulation.

A. Well, I think that that contains some information in the Piraccini abstracts that would be useful in the development of palonosetron by a formulator. The sequence of when that occurs is -- I don't know if that's the issue.

Q. Thank you.

Taking a step back in the development process to the -- what did we call that first box that involved the clinicians and the marketing people?

A. We didn't actually call --

THE COURT: Product profile?

THE WITNESS: Product profile, that's correct.

BY MR. O'MALLEY:

Q. Product profile. Thank you.

Returning to the product profile portion of the product development, do you have an opinion whether the Piraccini abstracts would have been useful to those people in selecting palonosetron over other antiemetics?

I mean, if you have no opinion, that's fine.
A. Yeah, I don't really have an opinion about that.
Q. Okay. Now, the Piraccini abstracts taken as a group relate to pharmacology and the clinical sciences, correct?
A. No, I don't believe so.
Q. You don't believe so?
A. No.
Q. What would you characterize that they pertain to?
A. Well, the Piraccini abstracts deal with Phase I clinical trials, which are typically safety trials where you also collect pharmacokinetic data; but they don't deal with the pharmacology of the compound, per se. They may give you some inference about the toxicology of the compound.
Q. My question was they relate to the pharmacology or clinical science. I might have said it in the opposite direction. Correct? They relate to clinical sciences?
A. Well, certainly. They're clinical studies.
Q. Okay. And, again, that's not your area of expertise, correct? The clinical sciences?
A. Well, I'm not an expert in clinical sciences; that's correct.
Q. Okay. Now, abstracts don't go through the rigorous peer-review process that a full publication would go through, correct?
A. They do not. They usually go through a review process,

but it's not --
Q. It's not as rigorous.
A. It's not as rigorous, no.
Q. And the Piraccini abstracts were never published as a full, peer-reviewed paper with the complete results of those Phase I trials, correct?
A. I was unable to find them.
Q. You looked for that?
A. I looked over all the literature I could find for palonosetron.
Q. Okay. Now, don't you agree that in the absence of a later complete peer-reviewed publication discussed in the data presented in the abstract "one's ability to draw any conclusion from abstracts is extremely limited."
A. Yeah, I think abstracts have the value that they have. I'm not sure by what you mean by any conclusion.
Q. So, you can't -- you don't disagree -- agree or disagree that one's ability to draw any conclusion from abstracts particularly that do not become full, peer-reviewed papers later is extremely limited?
A. Well, again, they have the value that they have. It's not the same value that a full, peer-reviewed paper would have.
Q. Well, let me ask it this way: Would you agree that there are a number of reasons why abstracts are unreliable?

A. I don't know that I would characterize them as unreliable. That's not the word I would use.

MR. O'MALLEY: Can we put up the Spilker declaration, please. And this is also in your book, but it's also on the screen.

BY MR. O'MALLEY:

Q. Do you understand that Dr. Spilker is an expert, testifying expert, for defendants in this litigation?

A. I'm not aware of Dr. Spilker.

Q. Okay. I'll represent to you that he is such.

And do you see in Paragraph 15 -- and, first of all, before we go there, do you see this is -- you've been an expert before in this and other litigations, correct?

A. I've been an expert in other litigations, correct.

Q. Okay. And do you see that this is a declaration prepared for the United States District Court for the District of Delaware?

A. That's what it says there, yes.

Q. And you may not know this, but -- you may or may not recognize that the stamp on its side in the right-hand column indicates that this declaration was, in fact, filed with the District Court of Delaware. Do you know that?

MR. WONG: Objection, your Honor.

THE WITNESS: I don't know that.

MR. O'MALLEY: That's fine.

BY MR. O'MALLEY:

Q. Now -- and let's turn to the last page. And you see that this was executed by Dr. Spilker?

A. Yes.

Q. Okay. Now, you see it in Paragraph 15 that it states that, second sentence, "Abstracts are well known to have serious limitations as to their validity and reliability in terms of accuracy and overall credibility."

Do you have any opinion one way or the other, do you agree with that?

A. I have no basis to agree with that.

Q. Do you have any basis to disagree with that?

A. I think that that's not the words that I would use to describe abstracts.

Q. Okay. Fair enough.

And if we turn to Paragraph 16, do you see where, beginning in Paragraph 16 Dr. Spilker opines that there are a number of reasons why abstracts are unreliable, and he goes on to articulate what those reasons in his view are.

Do you see that?

A. I see that he's -- I see that, yes.

Q. And do you agree or disagree or have any opinion with respect to Dr. Spilker's view why abstracts are unreliable?

A. No, I have no opinion. I haven't read it.

Q. You have no opinion one way or the other?

A. That's correct.
Q. So, you don't necessarily disagree with him, correct?
A. I have no opinion.
Q. Okay. Now, you testified about four Piraccini abstracts, is that correct?
MR. WONG: Judge, objection to the accuracy. There were three.
MR. O'MALLEY: Okay.
BY MR. O'MALLEY:
Q. Three or four. You testified about several Piraccini abstracts.
A. I testified about three, yes.
Q. And the Piraccini abstracts were published several times in slightly different forms, correct? The data was published in several different forms?
A. Well, I seem to remember that there were different data associated with some of them, yes.
Q. Okay.
A. There were various studies that were reported.
Q. Taken as a whole, the Piraccini abstracts do not contain any actual data demonstrating efficacy of the palonosetron compounds as an antiemetic, correct?
A. To the best of my recollection they commented on that as an intended use for their compound.
Q. They don't contain, though, any actual efficacy data; is

that correct?
A. To the best of my recollection, that's correct.
Q. Now, you also testified as to certain of Helsinn's press releases.
Do you recall that?
A. Yes.
Q. And you recall that, taken as a group, none of the press releases make reference to specific doses, volumes, or concentrations with respect to any palonosetron formulation, correct?
A. That's correct.
Q. Now, you've testified in deposition that you personally would have no purpose to rely on a press release in attempting to determine whether or not a drug product has efficacy; is that correct?
A. I don't recall saying that.
Q. Well, does that accurately reflect your view --
A. I'm sorry --
Q. -- that you would have no purpose in turning to press releases to determine whether a drug product has efficacy?
A. I don't know that that's true. I don't -- I don't necessarily agree with that.
THE COURT: Do you concern yourself with efficacy as a formulator?
THE WITNESS: Well, I mean, it's of interest to me.

I mean, it's not -- and certainly there is a utility in knowing what someone reports as being efficacious doses. That's useful information.

BY MR. O'MALLEY:

Q. Let's turn to the 4/30/2014 Kirsch Deposition Transcript, 193:6-12.

"QUESTION: Understood. But I'm asking specifically whether you've ever relied on a press release in attempting to determine whether or not a drug product has efficacy.

"ANSWER: I'm not sure for what purpose I would do that."

Did that accurately reflect your opinion at the time?

MR. WONG: Objection, Your Honor. I don't think that's impeachment.

THE COURT: I'll allow it.

BY MR. O'MALLEY:

Q. Did that accurately reflect your opinion at the time?

A. I believe so.

Q. Okay. Now, I'd like to talk to you about what we have been referring to Eglen, 1995, and that's DTX-0283.

Now, I want to make sure we understand precisely why -- what you're using this article for with respect to your opinions. You use it, in part, to support the obviousness of the claim concentration, correct?

A. That's correct.

Q. Okay. Do you assert that Eglen, 1995 would provide a clinician or marketing person a motivation to develop palonosetron as opposed to any other antiemetic compound? Is that part of your opinion regarding Eglen, 1995?

A. I don't have any opinion.

Q. You don't have an opinion on that.

A. No.

Q. So, is the only reason you're using Eglen, 1995 in support of your opinions -- to support your opinion regarding concentration?

A. Well, I mean, I think that that is part of the -- of what a POSA, a formulator, would understand from this manuscript. It would be useful for him in terms of defining concentration ranges.

I think the fact that Eglen and his colleagues were able to find potency and substantial potency would also be informative to a POSA with regard to the value of developing a palonosetron formulation.

Q. Okay. Okay. Now, concentration --

THE COURT: But the formulator that you're describing is not making the decision about whether it is valuable to make a formulation of a given drug or not. That formulator has the assignment to do it.

THE WITNESS: That -- that is correct. But it still would be of substantial interest.

MR. O'MALLEY: I'm sorry. I didn't hear the end of that answer. It would still be --

THE WITNESS: Of substantial, substantial interest to the formulator.

BY MR. O'MALLEY:

Q. Let me clarify. What would be of substantial interest to the formulator?

A. The pharmacology results that were seen with palonosetron.

Q. Okay. Now, again --

THE COURT: Why? Why? Because he wants to keep his job and wants to make sure that the project that he's on has a useful output, right?

THE WITNESS: Yes. I mean --

THE COURT: Outcome.

THE WITNESS: Yeah, as a member of a project team, you're always interested in what the clinicians and what the pharmacologists have to say and what -- you know, you get as excited about the compound as anybody does, so it's of considerable interest.

THE COURT: But when you're formulating, what you want to know is what are the characteristics of this drug that you're working with. That's what you're really looking for, right?

THE WITNESS: That's correct, your Honor. And also

the limitations in which you're going to be operating to manipulate the formulation.

THE COURT: Okay.

BY MR. O'MALLEY:

Q. Now, you referred to the POSA -- I'm paraphrasing -- wanting to know what the pharmacologists are looking at; is that correct?

A. Yes, correct.

Q. This is, in fact, an article that primarily deals with pharmacology, correct?

A. That's correct.

Q. And, again, you're not an expert in pharmacology, correct?

A. That's correct.

Q. Now, in terms of your obviousness opinions with respect to concentrations, first of all, concentration is just dosage divided by volume just to review, correct?

A. It is an amount divided by a volume.

Q. Amount of dose divided by the volume of that dose, correct?

A. Well, in terms of the concentration of the active drug ingredient, that's correct, yes.

Q. Okay. Now, again, in your career, you've never personally been responsible for selecting the active ingredient dosage amount in any drug product, correct?

A. I don't recall ever doing that, no.
Q. And this is more than pharmacology, it's actually preclinical pharmacology, correct?
A. Yes. This went as far as animal studies.
Q. Okay. And, again, preclinical pharmacology is not part of your expertise, correct?
A. I'm not a pharmacologist. That's correct.
Q. All right. Now, to determine the data that you referred to, in part, the authors of Eglen, 1995 conducted a so-called Bezold, B-E-Z-O-L-D -Jarisch, J-A-R-I-S-C-H, Reflex Test, correct?
A. Yes, I recall that.
Q. Do you recall that?
A. I recall that that's one of the tests that they conducted, yes.
Q. And in addition, the authors also conducted a chemotherapy-induced emesis ferret model test, correct?
A. Yes. Ferrets and dogs they conducted.
Q. And you anticipated my next question. They also used a chemotherapy-induced emesis dog model, correct?
A. Yes, that's correct.
Q. Now, the conclusions in Eglen, 1995 are that -- and this is DTX-0283.0006. Let's find the conclusions. And starting at "In animal models."
And it states, I'll start at the beginning of that

sentence, "The present study has shown that at least in animal models, RS-25259-197 represents a significant improvement over ondansetron as an antiemetic agent with respect to potency and degradation of action."

Do you see that?

A. I do see that.

Q. And, again, all of the conclusions and data from this publication are based on animal studies, correct?

A. That is correct.

Q. Now, Eglen also --

THE COURT: Counsel, if you don't mind, just -- I know it's your cross, but could you just read on a little bit more so that the thing is in context?

MR. O'MALLEY: Sure.

BY MR. O'MALLEY:

Q. Continuing, "It should be noted that granisetron has also been reported to possess some" --

THE COURT: The same.

BY MR. O'MALLEY:

Q. -- "the same advantages over ondansetron," citing Andrews et. al. 1992.

Do you see that?

A. Yes, I do.

Q. I was intending to read the next sentence, so I'll just continue.

A. Okay.
Q. "As the present study lacks extensive antiemetic efficacy data with granisetron, it is unclear as to how RS-25259-197 would compare with granisetron. Further studies should, therefore, be aimed at a direct comparison of the two drugs."
Do you see that?
A. Yes, I do see that.
Q. Now, when you went through your concentration calculation, you directly compared the two drugs, palonosetron and granisetron, using data from this article, correct?
A. For the limited purpose that we used that comparison, yes.
Q. So, you used this article for the purpose that the authors caution you that you should not.
Do you understand that?
A. No, I disagree with that characterization. The authors are simply saying that to nail down the relative value of those two compounds, there needs to be a side-by-side comparison.
The purposes that a POSA would use this study for were just to do some broad ranging of what concentrations might be useful to conduct their formulation studies. It was not to make a definitive decision about what the relative potency of the two compounds was.
Q. Well, in fairness, your POSA would not be making

decisions about dosages to take into the clinics, correct?

A. That's correct.

Q. Now, let's turn to PTX-0251. And this is a Minton publication dated 1994.

Do you see that?

A. Yes, I do.

Q. And it's entitled, "Volunteer Models For Predicting Antiemetic Activity of 5-HT_3 Receptor Antagonists."

Do you see that?

A. Yes.

Q. And do you see that it's from, or at least Dr. Minton is from the clinical pharmacology division of Glaxo Group Research.

Do you see that?

A. Yes.

Q. And, again, do you understand Glaxo is the group that developed granisetron?

A. I really didn't pay any attention to that.

Q. Okay. Now, ondansetron was the first 5-HT_3 antiemetic in the market. Do you know that?

A. I believe that's correct.

Q. Okay. Let's look at the last sentence of the first paragraph in the introduction. It states, "However, due to species' differences in pharmacokinetics and dynamic response, these methods may not give an accurate indication of the

antiemetic dose range of 5-HT_3 receptor antagonists in patients."

Do you see that?

A. I do see that.

Q. And we can go through this painstakingly if need be or if you don't recall, but do you recall that when the authors are referring to these methods, they're referring to the precise methods that Eglen, 1995 authors used to generate their data?

A. Um, it appears as though they were referring to some of the methods that were used, yes.

Q. Some of the same methods?

A. Some of the same methods. That's correct.

THE COURT: I see that Bezold-Jarisch up there.

MR. O'MALLEY: Right.

THE WITNESS: Yes, that's correct.

BY MR. O'MALLEY:

Q. And that's the rat test from Eglen, 1995, right?

A. That's correct.

Q. And they talk about ferret models, correct?

A. Yes.

Q. Now, you have no basis to comment on the authors' conclusion about the relative drawbacks of certain animal models they're referring to because you're not a pharmacologist, correct?

A. That is correct.

Q. Now, let's go back to Eglen, 1995 for a moment.

First of all, Eglen, 1995 was published about eight years before the 2003 filing date of the patents-in-suit, correct? The filing date being 2003, roughly eight years?

A. Yes.

Q. You agree?

A. Yes.

Q. Okay. Now, Eglen, 1995 is a publication by several Syntex authors, correct?

A. Yes, that's correct.

MR. O'MALLEY: Now, let's look at Eglen, 1996, DTX-0318, and let's go to the article itself. First page. Keep going. Okay. Let's go up the top, please.

BY MR. O'MALLEY:

Q. And you see at the top, this is a publication about a year later from the Eglen article that we were discussing earlier?

A. I see that Eglen is one of the authors of this article, yes.

Q. And you see it is dated 1996?

A. That's correct.

Q. And I'll read or actually paraphrase the title. It's "5-HT_3 Receptors:Molecular Biology, Pharmacology, and Therapeutic Importance."

Do you see that?

A. I do.
Q. And you understand this to be another publication by Syntex scientists?
A. Yes. It appears to be a review paper.
Q. And it's about one year after the article you relied on this morning?
A. That's correct.
Q. Now, let's look at DTX-0318-0008, and let's find the -- that sentence beginning "While." And I'll read it into the record: "While it's possible that their enhanced bioavailability and duration of action may afford some advantages, the use of higher affinity and longer acting 5-HT_3 receptor antagonists, as well as repeated administration of the antagonists, has only moderately improved the efficacy of 5-HT_3 receptor antagonists."

Do you see that?
A. Yes, I do see that.
Q. And do you have any basis to disagree with the authors' conclusion as to that class of compounds?
A. I think that's more of a speculation. I mean, I'm not sure it's a conclusion.
Q. As to their opinion, do you have any basis to agree or disagree with their opinion --
A. No.
Q. -- of that class of compounds?

A. No.
Q. I'm sorry?
A. No, I don't have any basis to disagree.
Q. Okay. Now, let's look at 0318.0009. In the first paragraph of the conclusions.
THE COURT: What article are we looking at?
MR. O'MALLEY: This is what's been referred to as Eglen, 1996. It's the article by the Syntex scientists, including Eglen as first-named author, a year after the article that was discussed this morning.
THE COURT: So, we're still in the same article that you just read from.
MR. O'MALLEY: Oh, yes, I'm sorry. That's correct.
THE COURT: Now we're to the conclusions page.
MR. O'MALLEY: Yes.
And let's find the sentence regarding NK-1 antagonists. Let's see. Let's go up to the first paragraph, first full paragraph.
BY MR. O'MALLEY:
Q. Okay. And it states that "Novel approaches to emesis, such as selective NK-1 antagonists, including CP-99,994, may prove to have greater efficacy in treating either delayed or 5-HT_3 receptor antagonist-resistant forms of emesis."
Again, it is the author's opinion, correct?
A. Yes, uh-huh.

Q. This is the opinion of Eglen one year after Eglen published that animal data. Did you see that?
A. Yes, it is a speculation. He says "may prove." So, he is speculating.
Q. He's speculating at this point in time in 1996 that NK-1s may have some advantages over the class of 5-HT_3s.
Do you see that?
A. That's what he's speculating, yes.
MR. O'MALLEY: Your Honor, this is a good time for the afternoon break if it's good for you.
THE COURT: Fine. Good suggestion. Thank you.
(Brief Recess.)
THE COURT: That's fine. Thank you.
BY MR. O'MALLEY:
Q. Dr. Kirsch, I want to back up a little bit to something I couldn't find earlier.
In terms of what would motivate a POSA, I believe you've testified that with respect to marketing or economic reasons, those might provide motivations to the product profile people but not to the POSA formulator, correct?
A. Yeah. Typically, the product profile is developed by marketing and clinical people.
Q. Okay. And those marketing or economic reasons would not typically motivate the work of a pharmaceutical formulator; is that correct?

A. Well, they might consider that motivation, but, you know, typically they're assigned the task.
Q. They're assigned the active ingredient, correct?
A. And the product profile, correct.
Q. And usually the dosage form, correct?
A. They are typically assigned a proposed profile for the dosage form so, you know --
Q. So --
A. -- as we described before.
Q. So, for example, whether it's going to be a tablet or an I.V., that would be assigned to them, correct?
A. Typically, yes, um-hum.
Q. And if a tablet, whether it's going to be immediate release or sustained release, that would be assigned to the pharmaceutical formulator, correct?
A. That would be a typical scenario, yes.
Q. Okay. Now, I asked you before, do you recall testifying in the Astra case that, among the motivations that would have motivated the POSA in that case from your perspective which, again, was a pharmaceutical formulator, those motivations included marketing or economic reasons. I believe you testified you didn't recall; is that correct?
A. I didn't recall my testimony or --
Q. Now, if we could pull up the Astra decision, please. Let's look at the first page first.

And you may or may not recognize the format of this document. I'll represent to you it's a legal decision, *AstraZeneca v. Anchen*, and specifically, you see it's an opinion, scrolling down the left-hand column, by Judge Pisano. Do you see that?

A. Yes, I do.

Q. Do you recognize this document?

A. I was shown this document at one of my depositions, I believe.

Q. Okay. You didn't -- you hadn't seen it before that?

A. I don't recall seeing it before that.

Q. All right. Fair enough.

Let's turn to Page 24 in the upper right-hand corner, and first paragraph. And you were providing a opinion regarding the motivation that a POSA would have had to try a sustained-release version of a existing drug product. Do you recall that?

A. I think -- you know, what I recall is largely described here, that a motivation existed for a sustained-release formulation.

Q. Because of marketing or economic reasons; do you recall providing that testimony?

A. Again, pharmaceutical companies sometimes either need to find a product to compete in a one-a-day market or to extend the life -- the product's life cycle.

Q. But, again, the POSA that you were testifying about in that case, like this case was -- the POSA was the pharmaceutical formulator, correct?
A. I was -- I was putting forward that definition, that's correct. I was putting forward that definition, that's correct.
Q. Okay. Let's --
THE COURT: Maybe, though, he was speaking about what pharmaceutical companies do in that portion of testimony rather than what the formulator POSA person focuses on. Do you recall, Doctor?
THE WITNESS: That's my recollection. I mean, you know, I was talking about what motivates a company to pursue a sustained-release dosage form.
BY MR. O'MALLEY:
Q. And was that part of your obviousness opinion in that case?
A. You know, I don't -- I don't recall the details.
Q. Do you believe in this case that what would motivate a company as a whole to pursue a specific drug product would be relevant to the obviousness issue in this case?
A. I think the obviousness issue in this case goes to what would have motivated the POSA in this case.
Q. Which is just your formulator?
A. That's correct.

Q. Okay. Now, let's talk -- we were talking about your dosage opinions. Let's turn to Tang DTX-0276. Now, before we get into the details, let's just review.

Let's look at Kirsch Demo 24.

Now, help me out. Is this the slide that has your -- no, no, no. I have the wrong demo.

A. I think it's the next one.

Q. Let's look at Kirsch Demo 25. Okay. This is the slide where you provided your obviousness position as to concentration based on the teachings, as you understand them, of Tang, correct?

A. Yes, this is where I describe how one would use the information in Tang to begin their investigation of concentration ranges.

Q. Okay. And, as you state in the heading there, Tang is a PONV Phase II study, correct?

A. Yes, that's correct.

Q. And that has clinical data, correct?

A. It does have clinical data.

Q. And, again, you're not an expert in reviewing clinical data, correct?

A. I'm not sure what you mean by reviewing clinical data.

Q. You testified --

A. I do review clinical data.

Q. Fair enough. Let me refine my question.

You've testified you're not a expert in clinical sciences, correct?

A. That's correct.

Q. Now, in this slide, you have a lower limit to the dose taught by Tang of .007. Do you see that?

A. I do.

Q. Now, you've provided four expert reports in this case, correct?

THE COURT: To the claim construction and two --

MR. O'MALLEY: No, not in claim construction. Let me help do the accounting.

BY MR. O'MALLEY:

Q. Two on the first three patents and two on the '219, all with respect to obviousness; is that right?

A. Yes, I believe that is correct, yes.

Q. Okay. And if there's more on claim construction, I don't recall those, but I'm just thinking about those four for the moment.

Now, in your final expert report, you provided some opinions about why Tang taught some efficacy for dosages lower than two mgs. Do you recall that?

A. Yeah, vaguely, I recall there was a section that discussed that, yeah.

Q. Do you recall by contrast that in your expert reports, up to that last one, the only dose that you discussed in your

expert reports as being effective from Tang, the teachings of Tang, was 2 milligrams?

A. Yeah, I -- I think that's true. I don't remember what the context of that discussion was exactly.

Q. Well, fair enough. Let's take a look at it. Let's look at the Kirsch 9-9-13 report, Paragraph 78.

Well, in fairness, let me read the bottom sentence. "Thus, a POSA would understand that targeted palonosetron concentrations from about .02 mg per mL to about 2 mg per mL would be suitable." So in fairness, I misspoke. You did talk about other concentrations. Do you see that?

A. Yes.

Q. Okay.

However, you state that the data in Tang, "demonstrated that the I.V. administration of palonosetron, 30 microgram per kilogram, 20 to 30 minutes before the end of surgery was effective in decreasing emesis in women undergoing major gynecologic surgery." Do you recall that?

A. I believe that that's what Tang said. This is a quote from Tang.

Q. In fact, Tang concludes, the authors conclude that that's the only dose that's effective in decreasing emesis. Do you recall that?

A. Yeah, in the limited context of Tang, in terms of the condition he was treating and the population he was treating,

that's what he concluded.
Q. That's what he concluded, that only that highest dose was effective, correct?
A. Right, within the context of the study he did, yes.
Q. Yeah.
THE COURT: Are we equating that dosage with the 2 milligram per milliliter figure in the last sentence?
MR. O'MALLEY: Oh.
THE COURT: In other words, the 30 figure --
MR. O'MALLEY: Yeah, yeah.
THE COURT: -- above is the same as the 2 milligram per milliliter.
MR. O'MALLEY: Thank you, Your Honor. I see where you're headed and you're correct.
BY MR. O'MALLEY:
Q. That, in fact, the only dose you picked out in this paragraph from the teachings of Tang as being effective is 30 micrograms per kilogram, correct?
A. Right. I base this calculation on that dose, that's correct, that's correct.
Q. Right. That's the only one --
A. That's correct.
Q. -- you cite to as being effective, right?
A. That's correct.
Q. And then you observe that --

A. Well --
Q. -- small volume parenterals could be from 1 milliliter up to a hundred milliliters. Do you see that?
A. Yes.
Q. And so then you divide that 30-microgram-per-kilogram -- which corresponds to a 2-milligram dose, approximately, correct? Correct?
A. That's correct.
Q. -- by those 2 milliliters to get your effective range of concentrations, right?
A. That does provide a range of concentrations.
Q. Okay. Well, that's what you believe the POSA would have targeted based on Tang, correct?
A. Well, I think the POSA might have anticipated that, ultimately, they would fall into that concentration range. I think for the purposes of understanding how concentration affects stability, they would have chosen a much wider concentration range than that --
Q. But again --
A. -- to begin their studies.
Q. -- getting back to my first point, the only dosage you seize on in your discussion of Tang here at least as being effective is the 2-milligram dosage, correct?
A. Well, again, this is a data point, so, yes, that's correct.

Q. And you're aware that Tang 1998 is the only peer-reviewed nonabstract publication containing human clinical data for the efficacy of I.V. solutions of palonosetron as of 2003?

A. Yes.

Q. Okay. And this dose, 2 milligrams, is eight times .25 milligrams, correct?

A. That's correct.

Q. And then let's go to your reply report, November 22, 2013. It's in your notebook if you need it, Paragraph 16.

And then in your summary discussion of Tang, once again, you state that "At least for PONV, Tang 1998 concludes that palonosetron 30 micrograms per kilogram I.V. was effective in reducing the incidence of PONV after major gynecologic surgery."

And, again, that was the only dosage in this report that you gleaned from Tang as being effective; is that correct?

A. No, I simply quoted what Tang said.

Q. Okay. But you didn't quote any other dosage from Tang as being effective in this report, correct?

A. No, I simply quoted Tang.

THE COURT: I'm sorry, counsel. Did you finish your answer?

THE WITNESS: Yes, I did.

THE COURT: Mr. O'Malley, would you please just give

the exhibit number? This is not in evidence. It's an expert report. It won't go into evidence but --

MR. O'MALLEY: That's correct.

THE COURT: -- I can't find it in your binder.

MR. O'MALLEY: Okay.

THE COURT: And so would you state the number for the record?

MR. O'MALLEY: Do you have that, Eric? It could very well be that --

THE WITNESS: I think it's on the screen.

MR. O'MALLEY: Oh, I wondered why they were gesticulating wildly. It's DTX-1006. Is it in the notebooks? Okay. Are you able to find it, Your Honor?

THE COURT: It's not in my binder that I've got, but I take your word for it. That's fine, and I'm not going to keep the binder anyway. I just wanted the citation --

MR. O'MALLEY: Okay.

THE COURT: -- because there are two reply expert reports from Dr. Kirsch.

MR. O'MALLEY: Correct.

THE COURT: The other one is in the binder.

MR. O'MALLEY: Okay. I can hand it up if it's of any use.

THE COURT: No, I'm following you.

MR. O'MALLEY: Thank you.

BY MR. O'MALLEY:

Q. This would be the reply expert report regarding the first three patents. Do you understand that, Dr. Kirsch?

A. Yes, I do.

Q. Okay. And in your deposition, do you recall agreeing that, "In the context of Tang's results," close quote, that the effective dose to treat emesis was on the order of about 2 milligrams? Do you recall that?

A. Yes, I believe that that's correct.

Q. Okay. And to get from the 2-milligram dose of Tang to the .05 mg per mL concentration of our early patent claims, you would have to use a minimum vial volume of about 40 milliliters, correct? I have a calculator if it helps.

A. Well, no, I don't need a calculator.

If you have 2 milligrams and you have a .05 milligram per mL concentration, then that statement is correct, that's true.

Q. Okay. Now, your opinion that small volume parenterals -- you call them SVPs; is that right?

A. Yeah, that's what they are called in the literature, correct.

Q. Okay. Can typically include volumes up from 1 milliliter up to a hundred milliliters, right?

A. Yes.

Q. And in your deposition, in discussing your opening expert

report, your first expert report, you testified that you rely on a reference by Dr. DeLuca for that teaching as to the range of typical volumes of SVPs. Do you remember that?

A. You know, I don't remember what reference we used. Certainly, that's not an uncommon value.

Q. Well, let's look at Paragraph 78 of your opening report, and the second-to-last sentence on Page 42. "For example," I'm quoting, "intravenous formulations, e.g. small volume parenterals, can typically include volumes from 1 milliliter up to 100 milliliters." And there is a Footnote 104. Do you see that?

A. Yes, I do.

Q. Let's go to Footnote 104. And do you see that you are citing -- your first cite is to a DeLuca reference. Do you see that?

A. I see that, yes.

Q. And you know Dr. DeLuca, correct?

A. I do know him, yes.

Q. He's had a distinguished career as a pharmaceutical scientist, correct?

A. Yes, he has.

Q. You consider Dr. DeLuca to be an expert in I.V. solutions, correct?

A. Yes, I do.

Q. And are you aware that Dr. DeLuca has been retained by

defendant Reddy's in this case?
A. I am aware of that.
Q. And are you aware of Dr. DeLuca's opinion on volume in this case?
A. I don't recall seeing that.
Q. And are you aware that he testified that if you want just a single use, then you're going to try to keep the volume low, 1 milliliter, 2 milliliters, up to 5. Are you familiar with the fact that he testified to that?
A. No.
Q. And are you aware that he also testified, "I wouldn't want to have somebody inject me intravenously directly with 5 mLs"? Are you aware of that testimony?
A. No, I'm not aware of that testimony.
Q. Are you aware, though, that the majority of the 5-HT_3 products that were available on the market in the 2002 and 2003 time period had volumes of roughly 1 to 2 milliliters?
A. I recall looking at the volumes that were associated with the other setrons that were on the market.
Q. And they were 1 to 2 milliliters; do you recall that?
A. Yeah, they were -- they were in that range, yes.
Q. Okay.
THE COURT: This raises just a passing question that I have had which is whether the formulators anticipate that if they create a vial for I.V. administration, it's going to go

directly into the blood vessel or it's going to go into the I.V. line that is already in the patient.

MR. O'MALLEY: Right.

THE COURT: I don't know.

MR. O'MALLEY: This isn't me, but previewing, I believe we will present evidence to the fact that most -- most physicians want a so-called single bolus injection. It's not often right into the vein, but they want to be able to draw it out, plunger it in.

THE COURT: Into what?

MR. O'MALLEY: Into that I.V. thing.

THE WITNESS: It's usually in a Y-site is usually --

THE COURT: In a what?

THE WITNESS: What's called a Y-site. They usually have a -- like a butter -- what's called a butterfly catheter that goes into a vein, and usually there's a Y-site there where there's two ports, one port that's open and the other port goes to a large volume parenteral to keep the vein open. And then what they would typically do is to inject the drug into the Y-site, which then goes directly into the vein, and that would be a typical way to administer these medicines.

THE COURT: So they don't -- they're not inserting it into the I.V. line that comes from the bag that's hanging on the hook? They're inserting it into a separate prong --

THE WITNESS: Right.

THE COURT: -- that's in the shape of a Y?

THE WITNESS: Well, that's correct. But the -- the I.V. line itself is also draining, so, you know, where they come together, so it --

THE COURT: They come together just before it enters the patient?

THE WITNESS: Yeah, a little ways, that's correct, Your Honor.

THE COURT: Okay.

BY MR. O'MALLEY:

Q. Now, the Tang authors were testing the --

THE COURT: But it was apropos of your comment that I wouldn't want 5 milliliters injected into me. If it's in an I.V. line, you don't know that it's flowing in, and it's diluted by the -- by the whatever --

MR. O'MALLEY: Yeah, I don't want to misstate what the doctors are going to say, but you're going to hear a lot more about that, just by way of --

THE COURT: But bolus does not refer just to putting a needle in somebody's arm. It refers to, that it is all being -- the vial is being emptied in one operation.

THE WITNESS: The distinction is typically the time period that it takes to inject, you know, so an infusion would be something that would occur over a longer period of time. They have what are called short-term infusions which may occur

over 30 minutes or even a little bit more, and then the bolus which occurs in a matter of minutes or even seconds.

THE COURT: Okay. That's good enough for now. Thank you.

MR. O'MALLEY: All right. Thank you. This is way beyond my knowledge.

THE COURT: And it may not come up, but you were talking about volumes.

MR. O'MALLEY: Yeah.

BY MR. O'MALLEY:

Q. Getting back to Tang, the Tang authors are testing -- were testing the efficacy of palonosetron to treat PONV, right?

A. That's correct.

Q. And you don't have any basis to dispute that the doses required for 5-HT_3 antagonists to treat CINV were usually greater than those required to fully treat PONV, correct?

A. I have no opinion.

Q. Because, again, you're not a pharmacologist or expert in clinical sciences, correct?

A. That's correct.

Q. Now, I want to talk to you about your opinions regarding chelating agents in the EDTA in particular. Now, nowhere in the publicly available prior art is there a disclosure of any instability problem specific to palonosetron, correct?

A. That's correct.
Q. And, likewise, the prior art does not disclose any formulation of palonosetron to which EDTA has been added for any purpose, correct?
A. No, there's no formulation, information in the prior literature about palonosetron specifically.
Q. Now, a formulator's goal will always be to develop the simplest formulation with the fewest excipients possible, correct?
A. In -- yes. I mean, that's correct. Any excipient that's placed in an injectable product has to be justified.
Q. It has to be justified.
A. That's correct.
Q. And a chelating agent would be such an excipient, correct? You would have to justify its presence in your injectable formulation?
A. Yes, you would.
Q. And by justify, you would have to show that it demonstrates some positive effect, correct?
A. That's correct. Or you would have to make the case that it's showing a positive effect.
Q. Now, it's true that, in some circumstances, chelating agents like EDTA can destabilize certain I.V. formulations, correct?
A. Well, to be honest, I don't know of any specific

instances, but it's conceivable to me that that could happen.
Q. Okay. Fair enough.
Now, before I get into Won, I want to drop back and talk about a couple more of your concentration-related demonstratives.
If we can go to Kirsch Demonstrative 23, please. Now, again, this slide is based on Eglen 1995, correct?
A. That is correct.
Q. And you're making a comparison based on predicted palonosetron to effective ondansetron dose, employing data from that article?
A. That is correct.
Q. And you recall by -- just to refresh our recollection, that the authors caution against using their data for comparisons of ondansetron and palonosetron. Do you recall that?
A. For the purposes of efficacy, yes.
Q. Okay. You're making a comparison for the purpose of what a POSA would predict as a concentration range for efficacy.
A. No, I'm not. I'm making a determination of what concentration range the POSA would investigate in terms of stabilizing the compound in the formulation.
Q. You believe that the dose of palonosetron is relevant only to stabilization?
A. Absolutely not. But the purpose of the POSA's

investigation at this point is to determine how best to stabilize a solution formulation. When the information becomes available about the effective dose, then that has to be worked in to the design of the formulation.

Q. So this dose that -- dose range that you've cited on this demonstrative has nothing to do with any expectation as to efficacy. Is that fair?

MR. WONG: Objection, Your Honor, on his concentration range. This slide is on the concentration.

MR. O'MALLEY: Let me -- fair enough. Let me restate the question.

BY MR. O'MALLEY:

Q. So the concentration range set forth -- set forth on your slide is based on your POSA's view of that range that would maximize stability and has nothing to do with expectations as to efficacy. Is that fair?

THE COURT: Excuse me. Just -- I'm really sorry, but I've been distracted and I can't follow the question.

MR. O'MALLEY: Okay. Let me try again.

THE COURT: No, we can just read back the question. But I think I need to be able to concentrate on it. And I was looking at the screen, also. And I do see that there is a .6 milligram predicted palonosetron dose on Kirsch Demo 23 that you're talking about. So it's not only concentration that the hypothetical calculation contains.

MR. O'MALLEY: So, I forget where we are now. Did you want to hear the question back, Your Honor?

THE COURT: Could the reporter read the question, the pending question?

(Question read back.)

BY MR. O'MALLEY:

A. And my answer to that question is, no, that the way in which the POSA is going to determine what the target concentration range is on some prediction of what the efficacy may be. But he's not making a decision about what the efficacy or the dose is. He's -- well, he's making a prediction, but he's not -- he's not making a decision about what the predicted dose is. He wants to be sure that he can get a concentration range that would cover what likely doses might be.

Q. Now, that gets me back to my first question. You're using to -- the Tang data -- let's go back to the line that Judge Cooper pointed out -- to predict the .6 milligram palonosetron dose for efficacy, correct?

A. To anticipate what the dose may be, right.

Q. For efficacy?

A. Right.

Q. And in doing that comparison between palonosetron and ondansetron, using the Eglen 1995 data, you're making a comparison that the authors expressly cautioned against. Do

you understand that?
A. No, I don't understand that. I think that the purposes of this -- of this exercise are not to make predictions about what the relative dose is. The purposes are to try to bracket what could potentially be the -- a dose. And they're using Eglen and Tang and whatever other information they have to try to come up with an idea of where to start.
Q. Okay. Now, again, you understand, and Eglen's based on animal models, correct?
A. I do understand that.
Q. And as of the time relevant to these patents, Tang is out, peer-reviewed, full publication with human data, correct?
A. Yes.
Q. Now, with respect to this range that you glean target palonosetron concentration range from Eglen, the bottom number is .006 mg per mL, right?
A. Correct.
Q. And that's about 10 times lower than .05 mg per mL, right?
A. Correct.
Q. And then the top of the range is about 10 times higher than .05 mg per mL, right?
A. Correct.
Q. So to go from this teaching to .05 mg per mL, you would have to select .05 out of that range.

A. You would have to optimize the concentration that provides a reasonable level of stability.
Q. And you don't argue that there's any teaching in Eglen, albeit animal data, to select .05 specifically out of that range, correct?
A. No, there's no teaching in Eglen that says to pick .05.
Q. Okay. Let's go to Demo Slide 24. And this is again a slide, if I understood it correctly, based on the teachings of Eglen 1995 animal data; is that correct?
A. That's correct.
Q. And you predict -- or you glean from the teachings, these teachings of Eglen 1995, that the target palonosetron concentration range should be .002 to .2 mg per mL; is that correct? That's what you have set forth on this demonstrative.
A. I'm sorry. Could you restate the question?
Q. Yeah. I'm just trying to summarize what I see here.
You've gleaned from the teachings of -- these particular teachings of Eglen 1995 you referred to, that they would target a palonosetron concentration range of .002 to .2 mg per mL, correct?
A. Yeah, they would use that as a -- as an approximate guide, that's correct.
Q. And the lower limit of this range is about 25 times less than .05 mg per mL?

A. That is correct.
Q. And the upper limit's about four times greater than .05 mg per mL?
A. That's correct.
Q. And you don't offer an opinion that there's any teaching in Eglen 1995 that would suggest in particular .05 to be selected within that range; is that correct?
A. That's correct.
Q. And then let's look at Kirsch Demonstrative 21. And I just wanted to clean this up to follow up on my objection.

Your opinions offered today with respect to four -- Point 4 in your slide have all been with respect to the concentration of .05 mg per mL and have not related to .25 mgs, correct?
A. Well, I think they relate to .25 mgs and 5 mLs.
Q. Well, then let me ask specifically, your opinions today, you understand that in the '219 patent, that .25 mgs is a separate limitation? Do you see that on the left?
A. I really don't read it that way, as a formulation patent that goes to stability. I see it as --
Q. Well, let's assume for the sake of argument or a hypothetical that the .25 mg is, in fact, a separate limitation of that claim. The teachings that you've offered opinions about today, you don't offer them for any opinion that .25 mg, in and of itself, would have been obvious to your

POSA; is that fair?
A. Yeah, I think -- taking your hypothetical, I think I would agree, yes.
Q. Okay. Thank you.
Now, let's turn to Won in DTX -- DTX-0315 is it? Yeah, 345. Okay?
You provided testimony about the Won reference, correct?
A. Yes, I did.
Q. Now, the date of this reference is 1994, correct?
A. I thought it was later -- yes, 1994, you're correct.
Q. And this is a setron that, for whatever reason, never made it through FDA approval, correct?
A. That's my understanding, yes.
Q. And in your search of the literature, did you see that there were a number of setron molecules in the 90 -- 1990s to 2000 period that never made it through FDA approval?
A. Yeah. I don't know how to characterize it. There were -- there was a long list of compounds that were in this class. Whether or not they were pursued as -- as -- whether or not project teams are formed and they went through a development process, I really don't know.
Q. Yeah. My question was whatever happened, they didn't make it to approval?
A. That's correct.

Q. Yeah.

THE COURT: I noticed -- I didn't mention it, but I noticed in one of these excerpts that Dr. Kirsch was shown that there was a list of about ten names of setrons that actually got names. Do you remember seeing that? You don't have to find it.

THE WITNESS: Yeah, I don't recall, Your Honor.

THE COURT: Yeah, there were about -- almost ten names --

THE WITNESS: Oh, really?

THE COURT: -- with setron in it. So I guess some of them got named and were not just numbers.

THE WITNESS: Oh, that could be, yeah.

MR. O'MALLEY: Dr. Amidon's going to be talking about that next week at some length.

BY MR. O'MALLEY:

Q. Let's take a look at the Won compound compared to palonosetron, and why don't we turn to the Amidon, October 25, '13 report, Paragraph 109. And if we can highlight the structures for -- maybe I have the wrong thing.

Why don't we go to your slide regarding the Won compound versus -- ah, thank you.

You see this is Kirsch Demo 14?

A. Yes, I do.

Q. And you've set forth here the -- a representation of the

molecular structure of palonosetron versus the Won molecule; is that correct?

A. Yes, that's correct.

Q. And, for the record, can you indicate again which is which?

A. So, the molecule that Won and his colleagues studied is RG 12915. Palonosetron is the 26259 compound.

Q. Okay. So the Won molecule is on the left; is that right?

A. That's correct.

THE COURT: Sometimes that's read as 25259, right?

THE WITNESS: I'm sorry, did I -- yeah, I think that --

THE COURT: It's hard to read.

THE WITNESS: Yeah, I'm not sure what that is.

MR. LOMBARDI: Just for the record, Your Honor, it is 25, just so that it's consistent in the record.

MR. WONG: The representation on Kirsch Demo 14, the right side, underneath does say RS-25259. The witness was having a hard time reading that.

THE WITNESS: Thank you.

MR. O'MALLEY: Okay.

BY MR. O'MALLEY:

Q. Now, why don't we leave that up.

Now, you agree that small changes in a molecule structure can affect its stability in solution, correct?

A. Yes, I agree with that.
Q. Now, you'll agree that the overall differences in structure between the Won compound and palonosetron are anything but small. Do you agree with that? They're large.
A. Well, I mean, there are obviously structural differences between the molecules. They have some chemical moieties that are similar.
Q. But if you had to characterize the similarity or lack thereof overall, they're rather dissimilar, correct?
A. Again, you know, that's a very relative thing, dissimilar to what? I mean, as compared to what?
THE COURT: Are they both setrons?
THE WITNESS: They are both setrons.
THE COURT: Why are they both setrons?
THE WITNESS: Because they have the same pharmacological activity.
BY MR. O'MALLEY:
Q. Now, do you recall providing expert testimony in the *Protonix* litigation, pantoprazole?
A. Vaguely, yes.
Q. Okay. Well, we'll get back to that.
Now, in your discussion of the Won molecule, you've focused on two sites of possible oxidative attack. Do you recall that?
A. I'm sorry. Say that again, please.

Q. In your discussion of the Won molecule, for example, in your expert reports and in your deposition testimony, you discussed two possible sites of oxidative attack at the molecule. Do you recall that?
A. No, I don't recall that.
Q. Do you recall that you testified that one site of the oxidative attack could be with respect to the benzofuran moiety?
A. I think that that is something that Won reported, yes.
Q. Okay.
A. I'm not sure that I reported that.
Q. Okay. But you recognize that Won reports that that's another site of possible oxidative attack?
A. Yes.
Q. Okay. And palonosetron does not have a benzofuran moiety, correct?
A. No, it doesn't.
Q. And you testified about the teachings that a POSA might glean from Won generally, correct?
A. Yes.
Q. And among those teachings, you testified to the effect that Won teaches that smaller concentrations are generally more stable. Did I get that correct?
A. Yes, that's correct.
Q. Okay. And in your expert report, when discussing that

conclusion -- why don't we go to Kirsch 9-9-13 report, Paragraph 100.

You state, "Specifically, with respect to the effects of drug concentration on the stability of RG-12195" -- and that's the Won compound, correct?

A. That's correct.

Q. -- "Won 1995 confirmed the general principle that the rate of autooxidation is proportional to the substrate concentration." Correct?

A. I believe that that's what Won stated in their article.

Q. And in, I guess, my lay terms, that means it's more stable at lower concentrations; is that a fair interpretation of that statement?

THE COURT: Well, it says it in the next sentence.

MR. O'MALLEY: Yeah, thank you.

BY MR. O'MALLEY:

Q. "As shown quantitatively in Fig. 4, the higher concentration oxidizes faster and levels off at a lower percent, whereas the lower one oxidizes slower and levels off at a higher percent." Do you see that?

A. I do.

Q. But going back to this general principle of the rate of oxidation being proportional to the substrate concentration, first of all, you have a footnote there, 129. Do you see that?

A. Yes.
Q. And if we drop down to Footnote 129 with respect to the discussion of that general principle, you -- you have in your footnote -- you're referring to Won 1995 at 102, citing Bateman, 1954; Betts, 1971; and Connors, 1986. Do you see that?
A. Yes, I do.
Q. And let's look at DTX-0345-0008. And let's find that passage we've been referring to. "It's been stated that the rate of autooxidation is proportional to the substrate concentration," and there's the same citation from your footnote. Do you see?
A. Yes, I do see it.
Q. And the Won authors cite Connors 1986 among those references, correct?
A. They do.
Q. And if you turn to the references section at DTX-0345-0011, the Connors 1986 reference is the book that is being referred to with respect to that section on substrate concentration. Do you see that?
A. That's one of the books, correct.
Q. And are you familiar with that book?
A. Yes, I am.
Q. Have you employed that book in your research?
A. Yeah, I mean, I've referred to that book.

Q. And do you see Dr. Amidon is one of the authors of that book?

A. Yes, I do.

Q. Okay. Now, getting back to this notion of structural similarity with respect to the Won and palonosetron molecules --

MR. O'MALLEY: Can we put those molecules back up from the Kirsch demonstrative, please.

BY MR. O'MALLEY:

Q. Now, it's true, isn't it, that a POSA can't know in advance without testing a formulation whether it will have the same or different stability as a formulation having a compound with a similar structure. That's true, isn't it?

A. Yes, that is true.

THE COURT: And do you test stability in your formulation research?

THE WITNESS: Yes, I do. That's a focus of my research.

BY MR. O'MALLEY:

Q. Now, let's take a look back at Amidon 10-25-13 report, Page 51, Paragraph 108, and let's go to the next page. Now, you see -- let's blow up those four structures.

You see that Dr. Amidon, in his report, discussed four setrons that I think were either on the market in the United States or in Europe. Do you recall that?

A. Yes, I do recall that he discussed these four compounds.
Q. And you reviewed his rebuttal report, I believe you testified to that.
A. I have reviewed it, yes.
Q. And, for the record, what's shown here are the chemical structures of tropisetron, dolasetron, azasetron, and granisetron, given the mispronunciations; do you see that?
A. Yes, I do.
Q. And you would agree with me that all four of these compounds have tertiary amines, correct?
A. Yes, they do.
THE COURT: They're shaped funny, aren't they?
THE WITNESS: Well, some of the -- you know, some of the -- some of the structures are a little different, some of them are simply drawn differently. I mean, they're certainly not identical.
THE COURT: And those -- but those are the -- sort of the uppermost appendages on these drawings, right?
THE WITNESS: Right. So we're looking at, you know, that is a tertiary amine. It has those two bonds and then this bond to what's a methyl group. This is a tertiary amine that's within that bicyclic ring structure, and then this one as well is within the ring, and then this one is also a tertiary amine, again, with the methyl group too.
Q. And for the transcript reader, Dr. Kirsch, you were just

identifying where the tertiary amine is located in each of these four setrons from this paragraph of Dr. Amidon's report, correct?

A. That's correct.

Q. Now, you're not aware of any literature or other evidence reporting any oxidation issues with respect to these four setrons, correct?

A. I think there is a report for granisetron where they did some oxidative stress tests and found some degradation products.

Q. Now, do you recall that in your deposition, you stated, "I don't recall seeing any literature on their instability"?

A. That's correct.

Q. So this is literature you've uncovered since your deposition?

A. Yes. When I saw these compounds earlier when you gave your opening remarks, I took a look in the literature, and there's a recent report.

Q. In any event, this recent report is not among the materials you've disclosed in connection with the opinions you offered in this case; is that correct?

A. Yes, that's correct.

THE COURT: And it wouldn't be prior art to these patents anyway.

THE WITNESS: It wouldn't be, yes. But I understood

his statement that it doesn't occur.

MR. O'MALLEY: That's a fair enough response.

BY MR. O'MALLEY:

Q. Now, I want to get into your reasonable expectations of success testimony. And that was your Demo Slide 27.

Now, you have a rather large "no" next to "Treating delayed emesis was an unexpected result." Do you see that?

A. Yes.

Q. And I believe you testified to the effect that -- I'm paraphrasing and please correct me -- that any delayed phase benefit would be due to the molecule and not what you view as the claimed invention; is that correct?

A. Yes, that's correct.

Q. And you're aware that there is an oral form of palonosetron on the market?

A. I -- yes, I am aware of that.

Q. Were you aware that it did not receive an indication for delayed phase emesis?

A. No, I'm not aware of that.

Q. Now, with respect to the second bullet, you were asked, "What about the second bullet," and I'm reading from the transcript, "What is your opinion as to whether or not the claim formulation has an unexpected pharmaceutical stability?"

And the answer was, "I don't believe that was unexpected result at all. I mean, that was the whole purpose

of the development process and that there was not an unexpected result."

Do you recall that?

A. Yes, I do.

Q. And that was the sum of your testimony with respect to that bullet. Do you recall that?

A. I believe it was, yes.

THE COURT: You're referring to this morning?

MR. O'MALLEY: Yes.

THE COURT: Direct, here?

MR. O'MALLEY: Yes.

BY MR. O'MALLEY:

Q. But, of course, the whole purpose of any development process will be to develop a pharmaceutical product with satisfactory stability; we can agree on that, correct?

A. Yes.

Q. And yet many fail, correct?

A. Not that I'm aware of.

Q. You're not aware of that?

Now, we discussed the opinions you gave in the *AstraZeneca v. Anchen* case earlier. Do you recall that? For example, your definition of POSA, et cetera.

A. Yes, yes.

Q. And you offered opinions in that case that the claims were invalid as obvious. Do you recall that?

A. That's correct.
Q. And at your deposition, my colleague discussed with you how Judge Pisano rejected your POSA definition, first of all. Do you recall that?
A. I recall our discussion of that, yes.
Q. And Judge Pisano also rejected your obviousness opinions as well, didn't he?
A. I believe that's correct.
Q. I'm sorry?
A. I said, I believe that's correct.
Q. In fact, the Court rejected your testimony because it was based primarily on hindsight, correct?
MR. WONG: Objection, foundation. I'm not sure the witness knows.
MR. O'MALLEY: Well, fair enough. Why don't we pull up the decision at star 40. And the Court finds that -- okay. So -- all right. Yeah, let's go back to that.
So the Court found, "However, the Court finds that such a conclusion" -- and, actually, let's back up so there's context to this.
BY MR. O'MALLEY:
Q. And towards the middle of the paragraph, "The Court finds that defendants have not met that burden. Defendants' experts testified that a POSA easily would have been able to make a HPMC-based gel system sustained-release formulation of

quetiapine in May, 1997. However, the Court finds that such a conclusion was based primarily upon hindsight and, further, failed to consider certain obstacles that a POSA would have faced in trying to develop any kind of a sustained-release form of a drug with the physical and biological properties of quetiapine."

Do you see that?

A. Yes, that is what it says there.

Q. And so you understand that the Court rejected you and the other defendants' opinions on the basis of hindsight?

A. That's what the statement says, that's correct.

Q. Thank you.

MR. O'MALLEY: I have no further questions.

MR. WONG: I'll try to be short, Your Honor, but I do have to cover a couple of issues.

THE COURT: Take whatever time you require, counsel.

REDIRECT EXAMINATION BY MR. WONG:

Q. Dr. Kirsch, do you recall Mr. O'Malley asking you about the *AstraZeneca* opinion in which you offered expert opinions?

A. Yes.

Q. Do you recall how many experts the defendants had in that case?

A. There were two experts, as I recall, that testified with regard to the formulation.

Q. So it wasn't just yourself that was offering expert

testimony on the formulation; is that right?
A. That's correct.
Q. And do you stand by your opinions in the *AstraZeneca* case?
A. Yes, I do.
Q. Did the *AstraZeneca* case cover the asserted patents in this case?
A. No, that was a much different case, where they were looking at the development of a sustained release oral form of a drug which was already on the market and an immediate-release form, and you know, in that circumstance, the excipients and formulations were really controlling the rate at which the drug appeared in the bloodstream, and so the conditions and the circumstances were much different than -- than for this simple I.V. solution formulation.
Q. Was palonosetron at issue in the *AstraZeneca* case?
A. No, it wasn't.
Q. And an intravenous formulation was not at issue in the *AstraZeneca* case?
A. No, it wasn't.
Q. With regard to marketing or economic drivers, was your opinion on those issues different than anything that you have here?
A. I don't believe so.
Q. What were the market and economic drivers that you opined

on in the *AstraZeneca* case?

A. Well, I think that I made the comments that a pharmaceutical company may seek to develop add-on formulations for product life extension, and obviously ones that have a therapeutic value or that they suppose has a therapeutic value and, you know, this is a typical process that's used in pharmaceutical companies to extend their product line.

Q. Is that inconsistent with your opinions in this case?

A. I don't believe so.

Q. Let's go to the '333 patent, DTX-0343.

THE COURT: Did you say extend the product line or extend the product life right now?

THE WITNESS: Well, the product line. The product life in a broad sense, right. Right. The life in that case, quetiapine products. Thank you, Your Honor.

BY MR. WONG:

Q. I want to follow up on a couple questions Mr. O'Malley asked you.

Do you recall Mr. O'Malley asking you to read off the list of possible dosage forms that could be used with the 5-HT_3 class disclosed in the '333 patent?

A. Yes, I recall that.

Q. And do you recall Mr. O'Malley also taking you to Example 13?

A. Yes, I do.

MR. WONG: If we can go to Example 13, which is on Page 15 and also continues onto Page 16. That's fine.

BY MR. WONG:

Q. Example 13 contains how many possible dosage forms?

A. There are three dosage forms there.

Q. And is one of the dosage forms an intravenous formulation?

A. Yes, one is an intravenous formulation.

Q. If you look at Example 13, Mr. O'Malley directed you to the amount of the Formula I compound in there?

A. Yes.

Q. And he made the analogy that there are -- sorry, it's the intravenous form -- 10 to 100 milligrams. Do you recall that?

A. Yes, I do.

Q. And he made the analogy that that was much higher than the claimed dosage of .25 milligrams. Do you recall that?

MR. O'MALLEY: Object to the form of the question. I don't know what an analogy means.

MR. WONG: A comparison.

THE COURT: Okay. That's fine.

BY MR. WONG:

Q. Does the '333 patent disclose anything about identifying the dose for the compounds disclosed in the patent?

A. No, it does not.

Q. Let me direct your attention to Page 7, and on Column 12,

the upper right-hand corner, the entire paragraph including the heading.

A. Oh, yes.

Q. What's the heading on the column?

A. So, this describes administration and pharmaceutical composition.

Q. Okay. And can you read that last paragraph starting at Line 19?

A. It says, "One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of a compound of Formula I for a given disease."

Q. Do you agree with that?

THE COURT: Counsel, the text immediately before that has a whole lot of numbers in it.

MR. WONG: Correct.

BY MR. WONG:

Q. Dr. Kirsch, can you give -- can you explain that last sentence of the first paragraph starting "therefore"?

THE COURT: No, it's -- before that, it's therapeutically effective amounts -- Dr. Kirsch has just, in answer to your prior question, said there aren't any dosages suggested in the '333 patent.

MR. WONG: Right.

THE COURT: And I'm just wondering whether those are dosages in that --

THE WITNESS: Yes, I misremembered. There is this section that relates to a effective -- potentially effective amounts of the compounds in Formulation I which, you know, they describe broadly as ranging from 1 nanogram per kilogram to 1 milligram per kilogram, so they do refer to potential doses.

BY MR. WONG:

Q. And after that disclosure of potential doses, the '333 patent includes a paragraph starting -- that you just read starting, "one of ordinary skill in the art."

A. That's correct.

Q. One last thing on the '333 patent. Mr. O'Malley suggested that the structure of palonosetron was not actually disclosed or contained in the '333 patent. Do you recall that?

A. Yes, I recall that.

Q. Can we turn to Column 9 which is on Page 6.

THE COURT: You said it was described in words, just not drawn.

THE WITNESS: Yes, that's correct.

BY MR. WONG:

Q. We can see at Lines 23 to 26, of Column 9. Dr. Kirsch, can you read that disclosure?

A. Yes, it says, "Of most interest are the compounds of Formula 1 in which p, q and u are 0, and R3 is the" quinuclidine, that's another name for it -- "in particular wherein one or, when present, both chiral centers possess an S configuration," which again just describes the three dimensional structure of the molecule.

THE COURT: If you say so.

THE WITNESS: Yeah.

BY MR. WONG:

Q. In this passage that you just read, does that describe palonosetron as of most interest?

A. Yes, it does.

Q. Do you recall Mr. O'Malley asking you about or showing you disclosures in the prior art regarding how 5-HT_3 receptors antagonists are generally regarded as the same? Do you recall that line of questioning?

A. State that again, please.

Q. Any disclosures that Mr. O'Malley showed you referencing an assertion that all 5-HT_3 receptor antagonists were the same in terms of efficacy?

A. Right, yes, I recall that.

Q. Can we go to Kirsch Demonstrative 19. And we reviewed this this morning, Dr. Kirsch, and I think the Blood abstract by Piraccini from 2001, can you read the highlighted sentence?

A. So, it says, that "Similarly, a long duration of action

may result from the long half-life and strong binding affinity," and it says that "a Phase II dose ranging study was initiated."

Q. Okay. How would that disclosure inform a POSA?

MR. O'MALLEY: Objection, Your Honor. If you recall as we went through those sections on the NK-1s, the sameness, he testified he had no basis to agree or disagree because that's not his specialty. So he has no foundation to do the same determination here.

MR. WONG: I believe the questioning -- I believe the questioning was on NK-1s. Dr. Kirsch has done an analysis on palonosetron and does have opinions.

THE COURT: If there are references in these references to equating the efficacy of various setrons, you would have to ask Dr. Kirsch something more specific to get back to that area of questioning, because he says all he knows about efficacy is what he reads on the page. He's not an expert in efficacy. Is that right?

THE WITNESS: I think that's fair, Your Honor.

MR. WONG: We can let another expert -- we'll have another expert on this issue.

THE COURT: Sure.

MR. WONG: We can move on.

THE COURT: Does that meet your objection, counsel?

MR. O'MALLEY: Yes, thank you, Your Honor.

BY MR. WONG:

Q. At some point this afternoon, Mr. O'Malley showed you a deposition -- transcripts from your deposition where I'm going to paraphrase a little bit, regarding press releases, and I think the question was: Have you ever relied on a press release in attempting to determine whether or not a drug product has efficacy? And your answer was: I'm not sure for what purpose I would do that. Do you recall that?

A. I recall that, yes.

Q. In your practice -- or would a POSA, in a POSA's practice, would they -- would he or she rely on a press release for some other reason besides efficacy?

A. Well, I think that the press release has some value, and -- inasmuch as it summarizes some of the work that's being done, so, and I think it shows, you know, a level of interest that -- that companies may have in a particular -- particular compound so, I mean, yeah, I think that it would typically have some value.

Q. And with respect to abstracts and the reliability of abstracts, have you in your own work relied on abstracts in performing formulation work?

A. Well, I have relied on abstracts and press releases, you know, you have to understand that in the pharmaceutical development world, there are not a lot of disclosures that are out there. And so you rely on the information that you can --

that you can obtain.

THE COURT: And then you test it all.

THE WITNESS: Yes.

THE COURT: Right?

THE WITNESS: That's correct.

BY MR. WONG:

Q. Okay. Do you recall Mr. O'Malley showing you a Minton reference, which is PTX-0257, I believe? Minton 1994. For the suggestion that the animal testing procedures in Eglen '95, including the Bezold-Jarisch reflex were unreliable?

A. Yes, I do.

Q. Do you recall that the Minton article was published in 1994?

A. I believe that's correct.

Q. And what was the date of the Eglen article?

A. The Eglen was in 1995.

Q. Okay. Let's go to Eglen 1995 which is DTX-0263 and let's look at the same two portions that you relied on in your direct which is on Page 5, in the upper right-hand corner.

This is the rat study that we relied on; is that correct?

A. That's correct.

Q. And Eglen, in fact, did do this study; isn't that right?

A. Yes.

Q. Okay. And we relied on that last sentence starting with,

"by the intravenous route"?
A. That's correct.
Q. We've seen this over and over again.
Dr. Kirsch, can you read the first sentence under this paragraph starting -- which is entitled "Studies on the Von Bezold reflex"?
A. The first sentence says --
THE COURT: Read it slowly, please.
THE WITNESS: Yes. "The inhibition of 2-methyl-5HT induced bradycardia is a useful test for the evaluation of 5-HT_3 receptor antagonists in vivo."
BY MR. WONG:
Q. So --
A. They make reference to this Von Bezold-Jarisch reflex.
Q. So would a POSA understand that at least the Eglen authors understood this test to be a useful test?
MR. O'MALLEY: Objection, Your Honor, foundation again. Dr. Kirsch was very forthcoming in testifying that his POSA couldn't really offer a separate opinion on these pharmacological tests.
THE COURT: He's not offering his opinion. The only question pending is, would this formulating POSA understand at least that the Eglen -- people who wrote the Eglen article understood this particular type of test to be useful. You may answer.

THE WITNESS: Okay, Your Honor.

I think that that's correct, that a formulating POSA would take the statement at face value and take it as an indication that the authors felt that it was a useful test.

THE COURT: Including the point that it makes in that paragraph which is that the palonosetron that they were studying appeared to be approximately threefold more potent than granisetron and 55-fold more potent than ondansetron, correct?

THE WITNESS: That's correct, Your Honor.

BY MR. WONG:

Q. Let's go to the other parts of the Eglen disclosure that you relied on in your direct. That would be on Page 6, the next page, the left-hand column, under the heading "Antiemetic Studies."

And do you recall that, in your slides, you relied on a sentence five or six lines down starting with, "The present study"?

A. Yes, I recall that, um-hum.

Q. And this study was done in the ferret and the dog model?

A. That's correct.

Q. And Eglen, et al., actually did this study. Is that your understanding?

A. Yes, it is my understanding.

Q. And what does the first sentence before this sentence

read?
A. So, the description of the method -- oh, the first sentence?
Q. Yes.
A. So, "The emetogenic effects of anticancer drugs is most pronounced with platinum drugs such as cisplatin."
Q. Can you read the next sentence?
A. Yes. "Cisplatin, when administered to dogs and ferrets, produces an emetic and behavioral profile which most closely resembles the clinical symptoms."
Q. So would a POSA reading Eglen also take that sentence at face value with regard to the veracity of the ferret and dog model tests?
A. I believe that they would, yes.
THE COURT: Veracity means truthfulness. Is that your question?
MR. WONG: Yes.
THE COURT: Not validity or anything like that?
MR. WONG: I believe I'm using it correctly.
THE COURT: Okay. Fine.
BY MR. WONG:
Q. Almost done.
Mr. O'Malley discussed volumes that you have used in your analysis this morning. Do you recall that?
A. That's correct. That's correct.

Q. And in your direct slides, you relied on the Broadhead reference?
A. Yes. That's correct.
Q. And what did you rely on the Broadhead reference for?
A. Well, one of the things that we relied on, in terms of the calculations, we relied on it as indicating that the pharmacopeial definition of a small volume parenteral was less than 100 milliliters.
Q. Okay. And in the excerpt from your expert reports that Mr. O'Malley showed you, you cited DeLuca --
A. Yes.
Q. -- again for the same proposition?
A. I did.
Q. Is that a standard definition for what a small volume parenteral is, 1 to 100 milliliters?
A. Yes, that's pretty standard.
Q. Okay. And can 100 milliliters be administered as a single-use unit-dose?
A. It can. You know, that's at the upper range, but it can.
Q. And why would a POSA consider volumes of --
THE COURT: What would that container look like?
THE WITNESS: Yes. Well, it could be a syringe pump, for instance, a very large syringe that was attached to a pump and go into the Y-site. So it -- it is certainly not the most convenient small volume parenteral, yes.

BY MR. WONG:

Q. Why would a POSA consider volumes between 1 and 100 milliliters when formulating an I.V. formulation of palonosetron that we discussed this morning?

A. So, you know, at this stage, they're looking for a broad range, and obviously they're going to try to narrow it down and they'll try to narrow it down so that it's the most convenient that it can be, but they're going to balance that with, you know, what they need to achieve stability.

THE COURT: Is there any standard kind of vial size for intravenous drugs?

THE WITNESS: Well, drugs come in, you know, for instance 1, 5, 20, 50 mL vials, and all of those sizes are found, are available.

BY MR. WONG:

Q. Let's talk about EDTA very quickly.

A. Yes.

Q. So does Won have a specific teaching as far as the commonality of EDTA as a chelating agent?

A. Yes, it does.

Q. And what does Won say?

A. Well, Won says that it's the most common chelating agent used in parenteral drug formulations or something to that effect.

Q. Okay. And in your own experience, when you suspect

oxidative degradation of a molecule in solution, do you typically screen for EDTA as a remedy?
A. Yes, we do.
Q. Have you ever not screened for EDTA in such situations?
A. In a formulation development process, no. Where we see evidence of oxidation, we always screen. That's one of the screens that we look at.
Q. Okay. Mr. O'Malley asked you about the 0.25 milligram dose --
A. Yes.
Q. -- in Claim 7 of the '219 patent?
A. Yes.
Q. Would a POSA rely on a person of skill, ordinary skill in the clinical sciences, with respect to the 0.25 milligram dose?
A. Yes, that's where they would -- that's what they would rely on to --
Q. Do you understand that in this case --
A. That's what they would rely on to settle on that dose.
Q. Do you understand that in this case, defendants have other experts that will provide testimony as to the 0.25 milligram dose in Claim 7 of the '219 patent?
A. That's my understanding.
MR. WONG: No questions.
MR. O'MALLEY: If we can put up DTX-0343 again,

Column 12. And let's go to that portion of the disclosure, I think it was around Line 16 to 18 that Mr. Wong was focused on. Let's go up a little bit. Just make it bigger. I need the stuff below that, too. Smaller, I suppose. Yeah, there you go.

RECROSS EXAMINATION BY MR. O'MALLEY:

Q. Now, you were just directed to this section of the disclosure starting at Line 19 that says, "One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance on personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of a compound of Formula I for a given disease." Do you see that?

A. I do see that.

Q. That person of ordinary skill isn't a pharmaceutical formulator, correct?

A. That's correct.

Q. Now, going above to the specific ranges that are disclosed here as therapeutically effective amounts, it starts at about Line 11, and they have successively narrower ranges. Do you see that?

A. Yes, I do. Excuse me.

Q. And the narrowest range of so-called therapeutic effective amounts is at the bottom, preferably, 700 nanograms per day to 7 milligrams per day. Do you see that?

A. Yes, I do.
Q. And how does that compare to, at both ends of that range, to .25 milligrams?
A. It's greater. It's greater than .25 milligrams.
Q. It's greater.
A. Oh -- yes.
Q. At the bottom, let's start with the bottom. How does that compare to .25? Nanograms is to the minus 9?
A. Oh, right, so maybe I misspoke. So that's .1, .7 --
MR. WONG: Your Honor --
THE COURT: I'm not going to hear an objection in the middle of the answer. Let him answer.
BY MR. O'MALLEY:
Q. How does 700 nanograms per day compare to .25 milligrams?
A. So, I have to go through the calculations, but that's .7 micrograms --
Q. Would you like a calculator? I can help you.
A. No, that's okay. I think I can do it in my head.
THE COURT: Do it in your head and then talk.
THE WITNESS: Okay.
BY MR. O'MALLEY:
Q. I have a calculator here if it helps.
(Pause.)
A. So I get about .05 milligrams per patient, assuming a 70-kilogram patient.

Q. I'm sorry. It's per day, sir.
A. Oh, you wanted to do it in days?
Q. Well, it's not per kilogram. Do you see the units?
A. Let's see. Oh, that's -- they've already adjusted for the patients.
Q. Yeah.
A. Wait, I'm sorry. I didn't see that. Right.
Q. It's .7 milligram, that lower number. Do you see that?
A. It's .7 micrograms.
Q. Well --
A. It's .7 micrograms.
Q. Why don't we conclude this failing exercise. It's a huge range. Would we agree on that?
A. Yes.
Q. And there's no particular teaching of .25 to the extent it falls within that range. Could we agree on that?
THE COURT: .25 milligrams.
BY MR. O'MALLEY:
Q. .25 milligrams, can we agree on that?
A. .25 milligrams falls within that range.
Q. There's no particular teaching as to pick out .25 milligrams out of that huge range as opposed to any other?
A. No, it just --
Q. Okay.
A. It just falls within the range.

Q. Okay. Thank you.

MR. O'MALLEY: I have nothing further.

MR. WONG: That's all we have for today, Your Honor.

THE COURT: Okay, fine. Thank you very much. Thank you for traveling all this way, and safe travels home.

THE WITNESS: Thank you, Your Honor.

MR. WONG: Your Honor, we have a list of exhibits. Can I hand it up to the Court?

THE COURT: Sure.

Mr. Wong, on behalf of defendants, has offered a list of exhibit numbers and they are admitted into evidence without objection, correct?

MR. O'MALLEY: And we -- no objection, Your Honor.

THE COURT: Thank you.

What do we -- I think we're ready to adjourn for the week. Yes?

MR. LOMBARDI: We certainly are, Your Honor.

THE COURT: Fine, wonderful.

MR. O'MALLEY: Agreed, Your Honor.

THE COURT: And we'll see you back here on Monday morning.

(The proceedings adjourned at 4:11 p.m.)

- - - - -

D

E

F

P

Q

R

T

U

V